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Clinical Handbook of Anxiety Disorders

From Theory to Practice

☼ Humana Press

Current Clinical Psychiatry

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Chapter 1
A Causal Systems Approach to Anxiety Disorders

Emma R. Toner and Donald J. Robinaugh

A Causal Systems Approach to Anxiety Disorders

Alice is a new patient at the clinic. During her first appointment, she describes her discomfort with meeting new people, her fears of embarrassing herself in public, and her tendency to spend hours replaying social interactions in her head. She says she blushes easily when she talks with friends, sweats too much in work meetings, and has difficulty falling asleep. More than anything, she feels alone.

As clinicians and caregivers, our first task in working with patients is to identify the cause of their distressing experiences. What is leading Alice to experience this particular constellation of symptoms?

One common approach is to assume that these symptoms are caused by an underlying disorder. For Alice, we would likely assign a diagnosis of social anxiety disorder, concluding that this disorder is the underlying cause giving rise to her symptoms. In other words, we would conclude that she fears interactions with strangers and avoids parties *because* she has social anxiety disorder.

There are limitations to this approach. For instance, psychiatric disorders are not easily separated from the symptoms that define them [1]. Whereas a patient exhibiting no symptoms can still be diagnosed with lung cancer, a patient with no anxiety in social situations cannot be diagnosed with asymptomatic social anxiety disorder. The subjective experience of social anxiety is a necessary component of the disorder [1]. In addi-

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© Springer Nature Switzerland AG 2020
E. Bui et al. (eds.), *Clinical Handbook of Anxiety Disorders*, Current Clinical Psychiatry, https://doi.org/10.1007/978-3-030-30687-8_1

tion, this approach treats symptoms merely as indicators of an underlying or latent condition. Yet, symptoms are at the core of psychiatric phenomenology and frequently constitute the chief problems for which the patient is seeking help. Moreover, symptoms may themselves have direct causal importance, affecting both other symptoms and other domains of the patient's life. For example, Alice sought therapy due to the intense distress caused by her fear of social situations and because avoidance – itself caused by her fear of social situations – was negatively impacting her life.

Recently, some clinicians and researchers have taken an alternative approach to conceptualizing mental disorders that embraces the importance of individual symptoms and their interconnectedness. In this approach, symptoms and the causal relations among them are the primary causal agents in psychiatric illness, interacting with and reinforcing one another [1, 2]. For example, Alice avoided unfamiliar social gatherings *because* of her anxiety about embarrassing herself in front of others. Her avoidance, in turn, exacerbated and perpetuated her anxiety. From this perspective, social anxiety disorder is not the cause of Alice's symptoms. Rather, the symptoms constitute social anxiety disorder, and the causal relationships among those symptoms are what lead them to cohere and persist as a recognizable syndrome *(Fig. 1.1)*.

Although radical in its potential to challenge psychiatric nosology and assessment, this "causal systems" approach aligns extremely well with common clinical practice [2, 3]. Prior research has suggested that both clinicians [4] and patients [5] believe there to be important causal relations among symptoms. First-line, evidence-based treatments for anxiety disorders, such as cognitive behavioral therapy, already implicitly recognize and target complex causal systems by honing in on how individual symptoms (e.g., anxiety) lead to others (e.g., avoidance) and thereby sustain one another. In fact, many existing models of anxiety disorders (e.g., [6–8]) have long suggested causal relationships among symptoms. We can thus conceptualize the causal systems approach not as an effort to supplant prior theory, but as a conceptual framework that informs and advances these preexisting models [9].

The aims of this chapter are twofold. First, we will examine anxiety disorders through a causal systems lens in an effort to explore this conceptual approach to
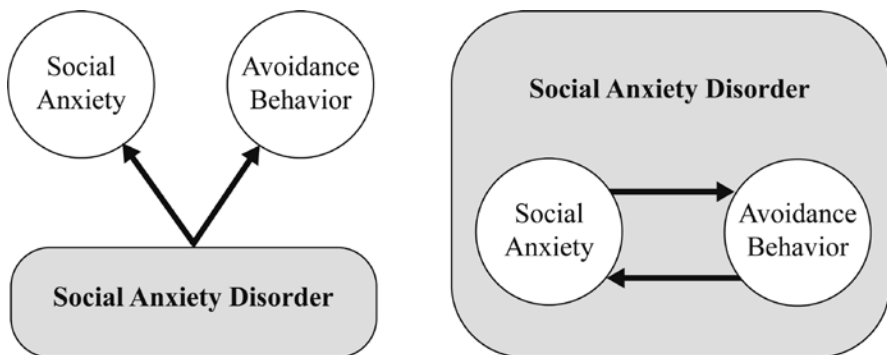

Fig. 1.1 Social anxiety represented from an underlying variable approach (*left*) and a causal systems approach (*right*)

their etiology and maintenance. Second, we will address how the causal systems approach can inform diagnosis and treatment of anxiety disorders and, in turn, its potential role in patient care.

A Causal Systems Approach to Mental Illness

At its core, the causal systems approach to psychopathology posits that mental disorders are best understood as systems of causally interconnected symptoms [1–3, 10]. The psychiatric diagnoses enumerated in diagnostic manuals such as the *Diagnostic and Statistical Manual of Mental Disorders* ([DSM]*,* [11]) provide valuable information about these causal systems [12]. As clinicians and researchers have long observed, psychiatric symptoms do not occur at random; rather, they tend to co-occur in relatively predictable groups, thereby forming the syndromes that constitute our current psychiatric diagnoses [13, 14]. From a causal systems perspective, causal relations among symptoms give rise to the symptom clusters that we recognize as syndromes. The DSM diagnoses thus identify symptoms that may operate together as a causal system. For example, the DSM-V diagnostic criteria for social anxiety disorder imply that avoidance of social situations is more likely to co-occur with fear of public embarrassment than it is fear of spiders, which suggests that there are plausible causal relationships between avoidance of social situations and fear of social situations [11, 13].

The Development of Anxiety Disorders from a Causal Systems Perspective

This picture of symptoms as dynamic, causal agents in a complex system raises the question: if there is no underlying cause, how does such a system come to exist? According to the causal systems perspective, a four-step process provides a general framework for thinking about how mental disorders develop [2]. Below, we outline this process and consider how it might specifically be used to understand the development of social anxiety disorder (Fig. 1.2).

Stage 1: Dormant System   Initially, the causal system is dormant: symptoms such as persistent anxiety about being embarrassed in social situations and avoidance are not active. Dormant systems exist in a state of *possibility:* although symptoms are not present, an external stressor may stimulate the system in such a way that a symptom or multiple symptoms can be activated.

Stage 2: Symptom Activation   One or more external stressors provide the initial activation of the causal system. These stressors can take many different forms, including adverse life events, environmental shifts, or biological changes, but are aligned in their ability to stimulate a previously dormant system by activating one or more symptoms in that system. For our example patient, Alice, the

Stage 1: Dormant System

Social Anxiety → Avoidance Behavior ⇄ Depressed Mood

Stage 2: Symptom Activation

Social Anxiety → Avoidance Behavior ⇄ Depressed Mood; External Stressor → Social Anxiety

Stage 3: Symptom Spread

Social Anxiety → Avoidance Behavior ⇄ Depressed Mood; External Stressor → Social Anxiety

Stage 4: Symptom Maintenance

Social Anxiety → Avoidance Behavior ⇄ Depressed Mood

Fig. 1.2 The suspected development and maintenance of Alice's social anxiety disorder through a causal systems framework

provoking event occurred almost a year ago when her supervisor chastised her in front of her coworkers in the middle of an important meeting. This experience was extremely distressing and activated her anxiety about speaking in a public setting.

Stage 3: Symptom Spread Because of the causal relationships among symptoms, this initial activation has the potential to initiate a domino effect as symptoms spread and more components of the system are activated. In the weeks following this upsetting event at work, Alice frequently ruminated and became increasingly self-critical, convincing herself that she was a terrible public speaker. As these thoughts persisted, she began to feel more anxious about the possibility of being asked to speak in work meetings and began to avoid taking on new projects at work for fear of having a similarly distressing experience. The more she avoided, the more she ruminated about her perceived shortcomings at work and she began to feel increasingly down and depressed.

Stage 4: Symptom Maintenance As time passes, the external stressor is often removed. For Alice, the memory of the highly embarrassing team meeting recedes into the past and no longer has a direct impact on her anxiety. However, the system has entered a new state. Rather than return to the dormant state the system was in prior to the stressor, the system has now entered an alternative stable state of persistent symptom activation. The cause of this activation is no longer the social stressor, but the symptoms themselves. In other words, the mutually reinforcing relationships among the symptoms are strong enough to maintain an active system state even in the absence of an external stressor.

It is at this juncture that we find Alice. As a result of her recently formed belief that social situations are dangerous, the possibility of any social interaction triggers anxiety and, in turn, a desire to avoid those situations. Avoidance then prevents her from having experiences that would contradict these beliefs, sustaining and exacerbating the anxiety that drives the avoidance. Moreover, her avoidance undermines her self-confidence, making her feel increasingly depressed. Her depressed mood, consequently, makes social situations feel all the more daunting, further exacerbating her avoidance.

Disorder and Comorbidity from a Causal Systems Perspective

From a causal systems perspective, a mental disorder is present when it has entered this fourth and final stage. Alice's symptoms of social anxiety disorder are present and self-sustaining. Moreover, the effect of these symptoms has extended beyond the social anxiety syndrome to include depressed mood. Over time, it is likely that her depressed mood would give rise to physical symptoms such as poor appetite, impoverished sleep, and low energy; symptoms like these would further exacerbate not only her depressed mood but also avoidance and, consequently, social anxiety. Thus, with time, Alice's self-perpetuating system would likely include symptoms of both social anxiety and major depression, inextricably intertwined and reinforcing one another.

As illustrated by Alice's experience, a causal systems perspective suggests that psychiatric comorbidity arises from the cross-syndrome spread of symptoms. This spread is possible because there is considerable overlap in symptomatology across psychiatric disorders, and diagnostic boundaries are notoriously fuzzy [1]. In one recent study, researchers found that all DSM-IV psychiatric diagnoses were connected to at least three other diagnoses by way of common symptoms [13]. Some, like depression, were connected to as many as ten [13]. In other words, psychiatric symptoms tend to cluster in predictable ways; however, some symptoms are characteristic of a number of mental disorders. As a consequence of their boundary blurring, these symptoms may render one more vulnerable to developing comorbid mental disorders. These symptoms that connect otherwise distinguishable syndromes can thus be thought of as *bridge symptoms*, or connecting points between symptom clusters that can help to explain psychiatric comorbidity [12, 14, 15].

As illustrated by Alice's case, when working with patients with anxiety, it is especially important to consider how other symptoms that commonly co-occur with

anxiety disorders, such as depressive symptoms, may contribute to the overall causal system. Recent research adopting the causal systems approach helps inform our understanding of these cross-syndrome relationships. For example, in a recent network analysis of social anxiety and comorbid depression, Heeren, Jones, and McNally [16] found that social avoidance was among the social anxiety symptoms most strongly associated with depressive symptoms [16]. Similarly, Beard et al. [17] identified the relationships between guilt and excessive worry as well as the relationship between sad mood and feeling nervous as important bridge pathways between the major depression and generalized anxiety disorder systems. These studies illustrate that there are important associations between the symptoms of distinguishable disorders that may contribute to their tendency to co-occur.

Beyond Symptoms

Although symptoms and the causal relationships among them are at the heart of the causal systems approach to psychopathology, this approach does not focus solely on psychological factors. The relationships among symptoms may occur through biological, psychological, or social mechanisms, and factors across these levels of analysis may impact the causal system. Indeed, from a causal systems perspective, psychiatric disorders may be best conceptualized as complex biopsychosocial systems [18]. For example, there is extensive evidence that social factors play a critical role (both protective and deleterious) in psychological illness (e.g., [19, 20]) and more recent studies have examined how anxiety disorders can, in turn, negatively impact social relationships [21]. In other words, the causal systems framework does not focus on psychological symptoms at the expense of considering biological or social factors. These components may play crucial roles in symptom maintenance, and addressing them may promote change in the primary psychological components of a patient's causal system. For Alice, it was a unique combination of biopsychosocial factors that contributed to her current mental state. A negative social interaction directly impacted her experience of anxiety, and subsequent avoidance took a toll on her social support systems at work. As she became more depressed, her appetite decreased and her energy lowered, further worsening her depression. Her physical, social, and psychiatric challenges impacted and reinforced one another and together contributed to her overall state of distress and impairment.

Individual Differences in the Propensity to Experience Anxiety Disorders

How did Alice get to this point? Many individuals would experience anxiety in response to being reprimanded by a supervisor without going on to develop an anxiety disorder. What makes this patient, and others who develop anxiety disorders, different from those whose anxiety is uncomfortable but transient?

Although we tend to conceptualize the presence or absence of mental disorder principally as a matter of whether symptoms are present or absent, a causal systems approach provides a more complex picture. Mental health is characterized not only by the absence of active symptoms but also by *weak* connections among symptoms that helps to sustain a stable state of minimal or no activation. When the causal relationships among symptoms are weak, an external stressor may produce activation in one or even many symptoms, but when the stressor is removed, the symptoms will subside as the causal relations among the symptoms are not capable of sustaining a high level of activation over time. Mental health is thus best conceptualized as a resilient system that returns to a stable state of minimal symptom activation even if temporarily perturbed by some external stressor. Indeed, the experience of anxiety in response to external stressors is normative and healthy. It is when that anxiety becomes chronic and disconnected from external cues that it becomes problematic.

From a causal systems perspective, mental disorder is characterized not only by elevated symptoms but also by *strong* connections among symptoms [2]. These connections produce a system at greater risk of settling into an alternative stable state of elevated and persistent symptoms over time: a pathological equilibrium in which the symptoms are self-sustaining [2]. Critically, it is the strength of the relationships among symptoms that plays the key role in determining whether such an alternative stable state is possible, as it is only when those relationships are strong that the system is capable of sustaining itself even in the absence of an external stressor [2, 14].

For Alice, there was a strong causal relationship between anxiety and avoidance; Alice quickly and repeatedly turned to avoidance as a strategy to combat the anxiety arising from her embarrassing experience at work. Not only did she lack alternative strategies for managing her anxiety, but the urge to avoid was so strong that it never occurred to her to consider other strategies. This strong effect of anxiety on avoidance put her at substantial risk for further symptom activation and, ultimately, a self-sustaining state of social anxiety disorder.

Consider another individual, Barbara, who experiences the same stressful and embarrassing event at work but exhibits a weaker relation between the symptoms of social anxiety and avoidance. Barbara would manage her anxiety without turning to avoidance (see Fig. 1.3), instead pursuing social interaction and rebuilding confidence in her ability to negotiate not just social situations but also the anxiety that can arise in those situations. Symptoms of anxiety may arise for a time, but the relationships among Barbara's symptoms would not be strong enough to produce a self-sustaining system in which anxiety persists after the stressor dissipates.

As the examples of Alice and Barbara illustrate, relationships among symptoms may differ across people. These individual differences in the structure of causal systems have two important implications. First, it is important to consider the strength of associations among symptoms. It is only when there are

strong relationships among symptoms that the system is capable of producing the sustained elevation in symptoms that we regard as psychopathology. Second, it is important to consider which associations among symptoms are most relevant for each individual patient. Patients may not experience every symptom of a psychiatric disorder and may report symptoms unaddressed by our current diagnostic tools. Some symptoms do tend to associate more readily than others, but the strength of these associations and the relative importance of each symptom to the system can vary across individuals. Accordingly, it is critical to consider which symptoms are at the core of a patient's particular symptom presentation.

For example, consider a third individual, Charlie, who confronts the same embarrassing event at work and experiences the same initial anxiety as Alice and Barbara. For Charlie, anxiety does produce some desire to avoid social situations, but also produces especially negative ruminative thoughts and, in turn, intense feelings of guilt and shame. His shame drives him to avoid social situations and, in turn, contributes to feelings of social disconnection. For Charlie, shame, rather than anxiety, is at the center of the mutually reinforcing symptoms. Although he shares many of the same symptoms as Alice, the driving force behind these symptoms differs between them *(*Fig. 1.3*)*.
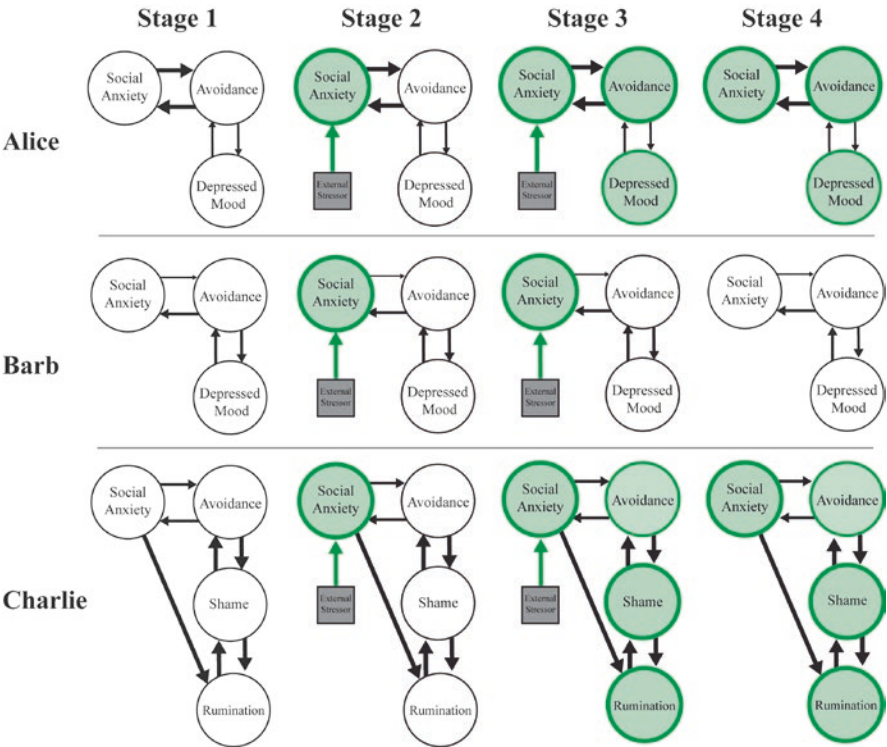
Fig. 1.3 Individual differences exist both in one's vulnerability to developing anxiety disorders and in the subjective experience of the disorder

Using a Causal Systems Approach to Diagnose and Treat Anxiety Disorders

From a causal systems perspective, therapeutic interventions can target specific symptoms (e.g., directly intervening on insomnia), factors external to the system (e.g., biological or social factors contributing to anxiety), or the casual relationships central to the functioning of the system (e.g., the relationship between anxiety and avoidance; [2]). Notably, many clinicians already conceptualize and diagnose anxiety disorders in a way that is in line this approach. They identify the symptoms causing patient distress, attempt to determine what gives rise to those symptoms, and, often, consider the function of the symptoms and how some symptoms may contribute to others [2, 22]. Cognitive behavioral therapies (CBTs) in particular place considerable emphasis on the feedback loops among cognitions, emotions, and behaviors that constitute the symptoms of anxiety disorders [23].

In Fig. 1.4, we outline the potential mechanism of action of CBT on an anxiety system. For Alice, primary CBT inventions involve directly targeting the causal
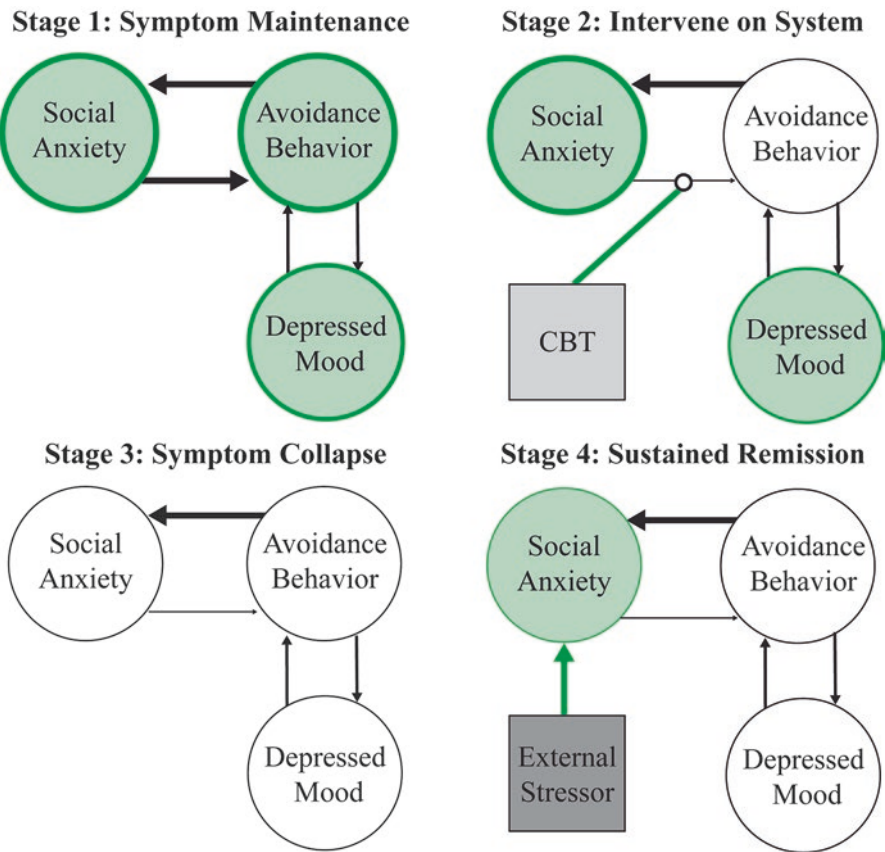
Fig. 1.4 Cognitive behavioral therapy (CBT) targets the causal relationships between symptoms in the causal system, working to minimize and, ideally, eliminate symptoms. Following treatment, Alice will exhibit greater resilience in the face of external stressors

effect of anxiety on avoidance by discouraging escape and avoidance behaviors in response to social anxiety. If successful, this intervention will have the immediate effect of reducing avoidance behavior. More importantly, intervening on this specific relationship may, in turn, lead to reductions in other symptoms and, ultimately, the collapse of the causal system. In the absence of the reinforcing feedback from avoidance behavior, the other symptoms will not sustain themselves, and anxiety and depressed mood will reduce in severity. For example, as Alice ceases to avoid, she will have opportunities to learn that the aversive consequences she anticipates from social situations either do not occur or are more manageable than she anticipated. Similarly, depressive symptoms will likely improve as she reengages in her social environment and has positive social experiences. Importantly, CBT aims to fundamentally alter the structure of the system, not just temporarily weaken relationships between symptoms. Following her course of CBT, Alice will ideally be able to experience similar stressors without her system again falling into an active stable state. Stressors are unpredictable and inevitable. Accordingly, it is critical to foster a resilient system by changing its overall structure, thereby increasing the likelihood that the patient can experience subsequent stressors without experiencing a relapse.

We suspect that the treatment of other anxiety disorders follows the same general framework of intervention we have outlined for social anxiety disorder. It is likely that anxiety disorder causal systems have similar motifs: recurrent building blocks that exist across disorders. For example, many theoretical models of anxiety feature a reinforcing feedback loop between anxiety and avoidance, in which the short-term relief afforded by avoidance comes at the long-term cost of increasing one's vulnerability to experiencing anxiety (e.g., [6, 8, 9]). Indeed, researchers have argued that this reinforcing relationship between emotional arousal and avoidance is a key feature across emotional disorders [24]. Accordingly, similar interventions and treatment strategies may be effective across anxiety disorders.

Recently developed transdiagnostic interventions, such as the Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders (UP), target symptoms across anxiety disorders through the same set of cognitive restructuring, behavioral interventions, and emotion exposure exercises [24, 25]. Implicit in these interventions is the notion that the structure of relationships among symptoms is consistent, even though the content may vary. Thus, intervening on these symptoms and inter-symptom relationships can lead to sustained system change (and, by extension, symptom remission). Recent randomized controlled trials testing the comparative efficacy of the UP to single-disorder protocols have provided support for this treatment [25], suggesting that transdiagnostic interventions for anxiety disorders may be equally as efficacious as disorder-specific interventions. From a causal systems lens, these findings lend credence to the theory that symptoms and the relationships among them, not latent diseases or diagnostic categories, are the crucial targets of intervention when it comes to psychiatric illness.

Beyond cognitions, emotions, and behavior, clinicians might also use a causal systems framework to consider how biological and social factors contribute to and change in response to a patient's symptom profile. Psychopathology is inherently

complex, and factors that initiate and maintain causal systems may be biological, psychological, or social [2, 12]. For example, poor sleep quality may worsen psychiatric symptoms and treatment engagement, further disrupting the patient's sleep [26]. Understanding the patient's medical history and social environment and how those factors interact with their presenting symptoms are important in developing a personalized and holistic case formulation.

Advancements in Causal Systems Research

As the previous section makes clear, the causal systems perspective does not propose an overhaul of clinical practice. Rather, it provides a new conceptual framework for understanding anxiety disorders, their persistence, and their treatment. In addition, this approach equips clinical researchers with tools from the rapidly developing interdisciplinary field of network science as they work to understand the structure and dynamics of mental disorder systems. These new directions for psychiatric research promise to expand our knowledge of the mechanisms and relationships underlying anxiety disorders and will hopefully point us in directions that ultimately improve patient care.

At present, two areas of causal systems research warrant particular attention due to their potential to advance clinical care. First, researchers are working on examining system structure and the unique roles that individual symptoms may play in the maintenance of specific syndromes. Much of this research has focused on identifying highly central symptoms in psychopathology systems (i.e., those with especially strong relationships to other symptoms; [16, 17, 27–29]). In the simple examples we have used in this chapter, the causal systems were comprised of only a handful of symptoms. However, in reality, patients may present with many symptoms across multiple syndromes, and it is not always clear which symptoms may be especially important to the maintenance of the syndrome. If researchers were able to identify which symptoms exert the most influence in an individual system, this information may be useful in determining ideal clinical interventions [2, 14, 15]. Second, researchers have also begun to turn their attention to studying intraindividual systems (i.e., the structure of the causal system as it exists within individual patients). The ultimate goal of this research is to closely examine patient-specific patterns of inter-symptom relationships in an effort to move toward a more personalized approach to psychiatric care [2, 30, 31].

To illustrate the value of this patient-specific understanding of the causal system and the role of individual symptoms within that system, let us return to Alice and Charlie. Both possess a causal pathway between social anxiety and avoidance behavior; however, Charlie's social anxiety is exacerbated and maintained by intense feelings of shame, whereas Alice's social anxiety is not. Thus, a traditional CBT intervention that relies solely upon exposure to feared social situations may initially be more effective for Alice than Charlie, as the effects of shame may impede Charlie's progress in therapy. Indeed, therapies – even those rooted in extensive

empirical evidence – are not "one size fits all." In order to fully benefit from treatment, Charlie will likely need to work with his therapist to address the role shame plays in his subjective experience of social anxiety. The promise of causal systems research is that it may someday assist clinicians in identifying the most suitable points of intervention for each individual patient.

Conclusion

In this chapter, we reviewed the causal systems approach to psychopathology and considered the implications of this approach in our understanding of anxiety disorders. From this perspective, symptoms, such as social anxiety and avoidance of social situations, are the key actors in anxiety disorders. Critically, it is the associations among these symptoms that lead them to persist and cohere as a syndrome. For individuals with weak relationships among symptoms, external stressors may lead to transient symptoms, but these symptoms will remit with time. However, for individuals with strong inter-symptom relationships, these symptoms will reinforce one another, and the system will settle into a pathological equilibrium of high symptom activation. For clinicians, it is critical to take a holistic approach to patient care, neither reducing the patient's symptoms to a single underlying disorder nor narrowly focusing on a single symptom. Instead, we must attempt to understand how symptoms work together in concert with other biological, psychological, and social factors to create this self-sustaining system. In doing so, mental health practitioners can target core aspects of the anxiety system to best meet patient needs.

References

1. Borsboom D, Cramer AOJ. Network analysis: an integrative approach to the structure of psychopathology. Annu Rev Clin Psychol. 2013;9:91–121. https://doi.org/10.1146/annurev-clinpsy-050212-185608.
2. Borsboom D. A network theory of mental disorders. World Psychiatry. 2017;16(1):5–13. https://doi.org/10.1002/wps.20375.
3. van den Hout M. Psychiatric symptoms as pathogens. Clin Neuropsychiatry. 2014;11(6):153–9.
4. Kim NS, Ahn WK. Clinical psychologists' theory-based representations of mental disorders predict their diagnostic reasoning and memory. J Exp Psychol Gen. 2002;131(4):451–76. https://doi.org/10.1037/0096-3445.131.4.451.
5. Frewen PA, Allen SL, Lanius RA, Neufeld RWJ. Perceived causal relations: novel methodology for assessing client attributions about causal associations between variables including symptoms and functional impairment. Assessment. 2012;19(4):480–93. https://doi.org/10.1177/1073191111418297.
6. Beck AT, Clark DA. An information processing model of anxiety: automatic and strategic processes. Behav Res Ther. 1997;35(1):49–58. https://doi.org/10.1016/S0005-7967(96)00069-1.
7. Jones JC, Barlow DH. The etiology of posttraumatic stress disorder. Clin Psychol Rev. 1990;10:299–328. https://doi.org/10.1016/0887-6185(90)90024-4.

8. Rapee RM, Heimberg RG. A cognitive-behavioral model of anxiety in social phobia. Behav Res Ther. 1997;35(8):741–56. https://doi.org/S0005-7967(97)00022-3 [pii]

9. Behar E, DiMarco ID, Hekler EB, Mohlman J, Staples AM. Current theoretical models of generalized anxiety disorder (GAD): conceptual review and treatment implications. J Anxiety Disord. 2009;23:1011–23. https://doi.org/10.1016/j.janxdis.2009.07.006.

10. Cramer AOJ, Waldorp LJ, van der Maas HLJ, Borsboom D. Comorbidity: a network perspective. Behav Brain Sci. 2010;33:137–93. https://doi.org/10.1017/S0140525X09991567.

11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington; 2013. https://doi.org/10.1017/CBO9781107415324.004.

12. Borsboom D, Cramer AOJ, Schmittmann VD, Epskamp S, Waldorp LJ. The small world of psychopathology. PLoS One. 2011;6(11):1–11. https://doi.org/10.1371/journal.pone.0027407.

13. Boschloo L, Van Borkulo CD, Rhemtulla M, Keyes KM, Borsboom D, Schoevers RA. The network structure of symptoms of the diagnostic and statistical manual of mental disorders. PLoS One. 2015;10(9):1–12. https://doi.org/10.1371/journal.pone.0137621.

14. McNally RJ. Can network analysis transform psychopathology? Behav Res Ther. 2016;86:95–104. https://doi.org/10.1016/j.brat.2016.06.006.

15. Goekoop R, Goekoop JG. A network view on psychiatric disorders: network clusters of symptoms as elementary syndromes of psychopathology. PLoS One. 2014;9(11):1–47. https://doi.org/10.1371/journal.pone.0112734.

16. Heeren A, Jones PJ, McNally RJ. Mapping network connectivity among symptoms of social anxiety and comorbid depression in people with social anxiety disorder. J Affect Disord. 2018;228:75–82. https://doi.org/10.1016/j.jad.2017.12.003.

17. Beard C, Millner AJ, Forgeard MJC, Fried EI, Hsu KJ, Treadway MT, et al. Network analysis of depression and anxiety symptom relationships in a psychiatric sample. Psychol Med. 2016;46:3359–69. https://doi.org/10.1017/S0033291716002300.

18. Kendler KS, Zachar P, Craver C. What kinds of things are psychiatric disorders? Psychol Med. 2011;41:1143–50. https://doi.org/10.1017/S0033291710001844.

19. Coyne JC, Downey G. Social factors and psychopathology: stress, social support, and coping processes. Annu Rev Psychol. 1991;42(1):401–25. https://doi.org/10.1146/annurev.psych.42.1.401.

20. Kessler RC, Price RH, Wortman CB. Social factors in psychopathology: stress, social support, and coping processes. Annu Rev Psychol. 1985;36:531–72. https://doi.org/https://doi-org.ezp-prod1.hul.harvard.edu/10.1146/annurev.ps.36.020185.002531

21. Hebert KR, Fales J, Nangle DW, Papadakis AA, Grover RL. Linking social anxiety and adolescent romantic relationship functioning: indirect effects and the importance of peers. J Youth Adolesc. 2013;42(11):1708–20. https://doi.org/10.1007/s10964-012-9878-0.

22. Persons JB. Cognitive therapy in practice: a case formulation approach. New York: W.W. Norton & Company; 1989.

23. Hofmann SG. Toward a cognitive-behavioral classification system for mental disorders. Behav Ther. 2014;45(4):576–87. https://doi.org/10.1016/j.beth.2014.03.001.

24. Farchione TJ, Fairholme CP, Ellard KK, Boisseau CL, Thompson-Hollands J, Carl JR, et al. Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. Behav Ther. 2012;43(3):666–78. https://doi.org/10.1016/j.beth.2012.01.001.

25. Barlow DH, Farchione TJ, Bullis JR, Gallagher MW, Murray-Latin H, Sauer-Zavala S, et al. The unified protocol for transdiagnostic treatment of emotional disorders compared with diagnosis-specific protocols for anxiety disorders: a randomized clinical trial. JAMA Psychiat. 2017;74(9):875–84. https://doi.org/10.1001/jamapsychiatry.2017.2164.

26. Carney CE, Edinger JD. Insomnia and anxiety. New York: Springer; 2010. https://doi.org/10.1007/978-1-4419-1434-7_3.

27. Bekhuis E, Schoevers RA, Van Borkulo CD, Rosmalen JGM, Boschloo L. The network structure of major depressive disorder, generalized anxiety disorder and somatic symptomatology. Psychol Med. 2016;46:2989–98. https://doi.org/10.1017/S0033291716001550.

28. Heeren A, McNally RJ. An integrative network approach to social anxiety disorder: the complex dynamic interplay among attentional bias for threat, attentional control, and symptoms. J Anxiety Disord. 2016;42:95–104. https://doi.org/10.1016/j.janxdis.2016.06.009.
29. McNally RJ, Robinaugh DJ, Wu GWY, Wang L, Deserno MK, Borsboom D. Mental disorders as causal systems: a network approach to posttraumatic stress disorder. Clin Psychol Sci. 2015;3(6):836–49. https://doi.org/10.1177/2167702614553230.
30. David SJ, Marshall AJ, Evanovich EK, Mumma GH. Intraindividual dynamic network analysis – implications for clinical assessment. J Psychopathol Behav Assess. 2018;40(2):235–48. https://doi.org/10.1007/s10862-017-9632-8.
31. Fisher AJ, Reeves JW, Lawyer G, Medaglia JD, Rubel JA. Exploring the idiographic dynamics of mood and anxiety via network analysis. J Abnorm Psychol. 2017;126(8):1044–56. https://doi.org/10.1037/abn0000311.

Chapter 2
Neurocircuitry of Anxiety Disorders

Carolina Daffre, Katelyn I. Oliver, and Edward F. Pace-Schott

Introduction

Although the *Diagnostic and Statistical Manual of Mental Disorders – 5* (DSM-5) has categorized each anxiety disorder based on its behavioral and subjective presentations, the neuroimaging literature suggests that biological mechanisms may be shared among the disorders [1, 2]. Generally, the neural activation of anxiety disorders can be categorized as either fear-driven activation or worry-driven activation [2, 3]. Fear-driven disorders are those that have a transient, fight-or-flight reaction coupled with hyperarousal to a distinct and immediate threat [2]. For example, specific phobia and social anxiety disorder (SAD) are fear-driven responses due to the clearly identified stimulus (e.g., spiders, snakes, crowds, etc.) accompanied by a disproportionately heightened state of arousal (e.g., racing heart, increased sweating, etc.) which dissipates once the stimulus is no longer present. On the other hand, worry- and stress-driven disorders are those which have more extensive periods of apprehension, worry, and despair over future or hypothetical situations that may not always be clearly defined [2]. In this chapter, we will first discuss the main experimental paradigms used to explore the neural mechanisms of anxiety disorders in both rodents and humans, discuss the basic

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functions of each structure implicated in these disorders, and then explore the role each structure is currently believed to play in specific disorders.

There are several experimental paradigms used to observe neural activity in anxiety disorders. Those paradigms usually fall under three categories: neutral-state paradigms, symptom-induction paradigms, and cognitive-activation paradigms. In neutral-state paradigms (e.g., resting-state fMRI), participants are often performing a continuous, idle task (e.g., staring at a white cross). Such paradigms are able to capture differences in brain activation between healthy individuals and individuals suffering for anxiety and stress disorders in the absence of triggering stimuli. Conversely, symptom-induced paradigms aim to measure brain function while an individual's symptoms have been purposefully induced (e.g., showing an image of a spider to someone with arachnophobia). This allows for the comparison of healthy and anxious individuals in order to determine physiological differences in the induced state. Lastly, cognitive-activation paradigms aim to induce activation of a specific neuropathway through carefully designed tasks. All three paradigm types are used with neuroimaging techniques measuring blood flow or blood-glucose levels as indices of brain activity such as positron emission tomography (PET), trace-guided single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI [4]).

One important distinction to bear in mind when reading fMRI studies is the difference between regional activation and resting-state functional connectivity. "Activation" of a brain region indicates that this area is more (or less) active in one condition (e.g., when viewing a stimulus) versus another (e.g., when viewing a black screen). This is termed a "contrast," and the quantity contrasted is the blood-oxygen level-dependent (BOLD) MR response that is proportional to the relative amounts of oxygenated and deoxygenated hemoglobin of the blood in that area. Activation can then be compared between groups (e.g., panic disorder vs. controls) by comparing their contrasts to the same pair of conditions. On the other hand, resting-state functional connectivity (rsFC) refers to networks of two or more regions of the brain whose BOLD signals fluctuate in synchrony at very low frequencies (e.g., 0.01 and 0.1 Hz) when a research subject is lying quietly awake looking at a fixation cross [5]. It is the degree of synchrony in such oscillations between two or more regions that is being compared when rsFC differences between different groups are being evaluated. Several studies have demonstrated that brain areas that are highly correlated in function will also have highly correlated BOLD signal changes during rsFC (for more details and clinical applications, see [5–7]). Of note, differing from both of these methods is "psychophysiological interaction" or PPI, an activational measure in which the degree to which different areas activate together during a particular contrast is assessed.

The fear-conditioning and extinction paradigms are among the most commonly used cognitive-activation paradigms in the neuroimaging of anxiety and stress disorders (see [8–10] for reviews). These paradigms rely on Pavlovian conditioning and extinction in order to experimentally mimic these processes. Fear conditioning involves the repetitive presentation of a stimulus which does not elicit an inherent fear response (e.g., a blue light), also known as the conditioned stimulus (CS), with

an inherently fearful or unpleasant stimulus (e.g., electric shocks; an unconditioned stimulus or US). Over time, the previously neutral stimulus alone is able to elicit a fearful conditioned response (CR) from the subject (e.g., increased heart rate, skin conductance response). Fear extinction, in turn, is when the CS is repeatedly presented without the US, signaling that the US will no longer follow the CS. Over time, the CS will no longer elicit the CR. Of importance to the treatment of anxiety disorders is the fact that extinction represents a new, inhibitory memory that competes with the conditioned fear memory when the CS is again encountered [8, 11, 12]. Which memory prevails determines whether or not fear will be expressed [13, 14]. Fear-conditioning and extinction paradigms have demonstrated robust and reliable responses in laboratory settings and have been instrumental in mapping potential brain regions necessary for fear and extinction acquisition and memory in both animals and in humans [8, 15]. Some of the structures implicated in the fear-acquisition process are the amygdala, dorsal anterior cingulate cortex (dACC), insular cortex, and hippocampus [3, 16]. Extinction learning and memory on the other hand involve the ventromedial prefrontal cortex (vmPFC) in addition to the hippocampus [3, 8, 11, 17]. Although these findings have served as a foundation for exploring the neurocircuitry of anxiety disorders, the role of the aforementioned structures in individual disorders is still under investigation (e.g., [18–20]).

In anxiety disorders and mood disorders with anxious features, stressors may trigger an enhanced activation of the limbic-hypothalamic-pituitary-adrenal axis (LHPA), the sympathetic nervous system, and other central stress mechanisms [3]. Studies suggest that activation and inhibition of stress responses are governed by the same structures identified in fear-conditioning and extinction paradigms (e.g., vmPFC, dACC, dorsomedial prefrontal cortex, insular cortex, amygdala, and hippocampus) [2, 21]. However, activation of the LHPA does not always occur during fear conditioning, and fear is not normally reported at other times when the LHPA is activated (e.g., when eating a meal or feeling nauseated [22, 23]). Therefore, overlap in structural activation does not imply functional overlap, and it is important to note that the same brain structures may have different functions in the manifestation of different anxiety-related disorders [2, 3, 22]. In order to better understand how this may happen, we will look at how the main structures implicated in anxiety disorders (i.e., the amygdala, anterior cingulate cortex, insular cortex, hippocampus, and ventromedial prefrontal cortex) may predispose individuals to anxiety disorders.

Brain Structures Implicated Across Anxiety Disorders

Amygdala

Several studies support the hypothesis that overactivation of the amygdala may be the primary culprit in anxiety disorders. As seen in Fig. 2.1, the amygdalae are located above the hippocampus in the ventromedial portion of the temporal lobe. Generally, the amygdala is involved in the processing of emotionally valanced
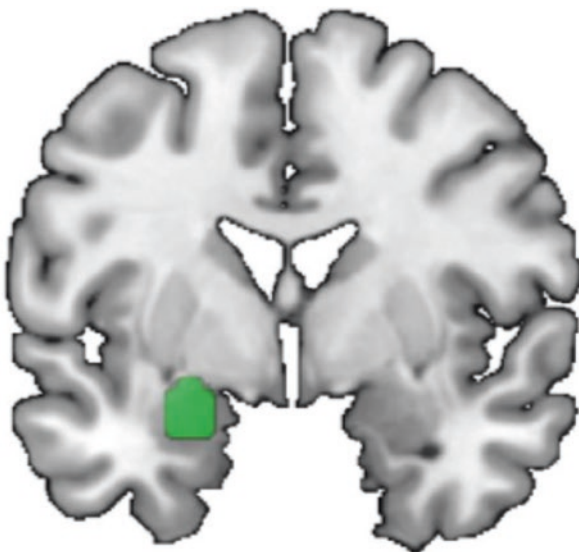
stimuli, especially aversive stimuli. The amygdala has been shown to reliably activate during tasks requiring the perception of fearful stimuli and cues predicting aversive outcomes, as well as the encoding and expression of fear behaviors [22, 24]. This makes the amygdala not only critical for information processing but also makes it one of the brain's key relay stations for anticipatory, avoidant, and fear-related behaviors. Several studies have shown that amygdala sensitivity to negative stimuli may be affected by the specific alleles of the 5-HTT-linked polymorphic region (5-HTTLPR) of the serotonin transporter gene carried by an individual [25]. The short and long alleles of 5-HTTLPR differentially affect amygdala sensitivity to dangerous environmental stimuli with individuals carrying the short allele being more reactive [26]. Another study found that those carrying at least one short allele showed greater amygdala reactivity when faced with social provocation (i.e., giving a speech to a public and private audience of study staff), with those homozygous for the short allele showing yet greater amygdala reactivity [27]. Interestingly, another study found that the short form of 5-HTTLPR is not only associated with hyperactivation of the amygdala but those carrying it also showed increased activation of the entire pathway implicated with threat anticipation [28]. These findings provide strong support for the genetic basis of psychopathology. Nonetheless, the 5-HTTLPR polymorphism may not be the only etiological factor leading to pathological functioning of the amygdala. During adolescence, an emotionally critical developmental period, the amygdala is naturally hypersensitive in order for humans to learn the social rules and emotional consequences of their environments [22, 29–31]. Studies show that pathological anxiety may arise when this hyperactivity fails to attenuate at the end of early adulthood [30]. Even individuals with non-pathological levels of anxiety, such as those who report higher state anxiety, dem-

onstrate increased amygdala activation to fearful facial expressions compared to neutral facial expressions [32]. Together, these findings begin to elucidate how the non-pathological functions of the amygdala may predispose some individuals to the development of anxiety disorders.

Bed Nucleus of the Stria Terminalis (BNST)

The BNST, located just above the amygdala, is part of a neural circuit termed the extended amygdala, and, like its neighbor, is implicated in the processing of negatively valanced emotional stimuli [33, 34]. There is increasing evidence that this structure is involved in the etiology and symptoms of anxiety disorders due to its prominent role in sustained and anticipatory fear and anxiety states [35]. The BNST projects directly to the hypothalamus and brainstem, mediating autonomic and behavioral responses to stress [36]. Lesion studies suggest that fear conditioning remains partially intact following bilateral damage to the amygdala suggesting a role for the BNST as a compensatory circuitry for fear processing [37, 38]. From these findings, researchers postulate that the BNST may be involved in anxious and avoidant responses that are slower in onset and longer-lasting in duration, making this structure a potentially key player in the maintenance of generalized anxiety disorder (GAD) symptoms [36]. Its role is often contrasted with that of the amygdala which generates acute fear responses, whereas the BNST generates sustained anxiety and threat apprehension [35].

Anterior Cingulate Cortex (ACC)

Although literature on the ACC is not as extensive as that on the amygdala, early research in cats and rodents has demonstrated that the ACC is involved in a large array of cognitive emotional and behavioral processes, including error detection, conflict monitoring, sensory and motor control, regulation of endocrine and autonomic functioning, processing of nociceptive stimuli, assessment of emotional content and valence, emotion regulation, and social cognition [39–41]. As one might expect, the anterior cingulate cortex is also strongly connected to the amygdala and medial prefrontal cortex (mPFC [3, 40]). In fact, due to the large and heterogeneous nature of the mPFC and the ACC, earlier studies may have characterized activation in these regions simply as mPFC activity. One meta-analysis exploring this issue in anatomical specificity indicated that most study results reporting PFC activation converged into two, specific subregions of the ACC, suggesting that these regions are also critical for emotion regulation [42]. The ACC can be divided into at least three distinct regions: the dorsal anterior cingulate cortex (dACC), the rostral anterior cingulate cortex (rACC), and the subgenual anterior cingulate cortex (sgACC).

Dorsal Anterior Cingulate Cortex (dACC)

Among its many functions, the dACC is involved in the modulation of attention (particularly to novel stimuli), sensory response selection, complex motor skills, and anticipation of taxing activities and nociception [41]. It has been argued that the function of the dACC is, in most general terms, the perception and processing of both physical and psychological distress in order to initiate survival-relevant behaviors [43]. Interestingly, the dACC has been reported to coincidentally activate in fear-conditioning studies designed to target the amygdala [44, 45]. Furthering these findings, Milad et al. [46] showed that healthy (non-anxious) individuals with greater thickness of the dACC had higher galvanic skin response (GSR) readings, during a fear-conditioning task. Furthermore, dACC activation was greater during presentation of the conditioned stimulus than of the innately fearful stimulus, suggesting that the dACC may play a role in the expression of psychophysiological fear responses [46]. In resting-state studies, the dACC is considered a major component of the "salience network," a group of structures also including the amygdala and insula that function to direct attention toward goal-relevant and other salient stimuli, such as those that evoke fear [47], that also contains central regulators of autonomic arousal [48].

Rostral Anterior Cingulate Cortex (rACC)

In contrast to the dACC, the rACC has been shown to be involved in regulation and assessment of, as well as response to, emotionally valanced and motivational stimuli [41]. In two versions of a Stroop-type interference task, one with cognitive interference and the other with emotionally salient interference, greater activation of the rACC was seen in the task containing the emotionally salient interference task [49]. The rACC has been shown to be involved in the suppression of emotional responses (both pleasant and aversive [50]). As previously mentioned, activation of the ACC has been strongly correlated with activation of the amygdala since the early days of research in this region, which we now know is mostly accounted for by activation in the rACC [40]. Moreover, Etkin et al. [51] demonstrated that the rACC may directly inhibit amygdala activation, as shown by simultaneous decrease in amygdala action as activation of the rACC increases during resolution in an emotional-conflict task. Thus the rACC is considered a key structure participating in top-down control of amygdala activity and accompanying emotional arousal [52, 53].

Subgenual Anterior Cingulate Cortex (sgACC)

The sgACC, a region of the ACC lying below the genu of the corpus callosum (Fig. 2.4) and corresponding to Brodmann Area 25, plays a prominent role in anterior cingulate control of autonomic and homeostatic processes [54]. The sgACC is

Fig. 2.2 Sagittal rendering
of the dorsal anterior
cingulate cortex
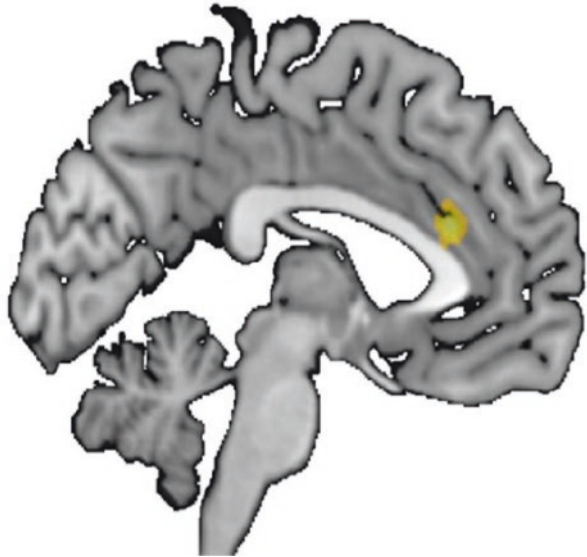
best known in psychiatry for well-documented abnormalities of this region in major
depressive and bipolar disorders [55] and as a target for deep-brain stimulation to
treat major depression [56]. Nonetheless, it has also been linked to symptoms of
anxiety-related disorders [57] and anxious personality traits [58]. The sgACC is just
caudal to but probably not functionally similar to the vmPFC, a structure key to
extinction learning and memory (see below), although some studies have shown a
degree of overlap [59]. Mayberg [60] demonstrated that greater activity of the pos-
terior subgenual vmPFC is associated with greater MDD severity and where others
have shown that posttreatment MDD patients have decreased posterior, subgenual
vmPFC activity [60–63].

In summary, it appears the dACC (Fig. 2.2) may be implicated in fear acquisition
through appraisal of threatening stimuli and arousal, while the rACC (Fig. 2.3) is
implicated in regulation of fear through top-down inhibition of fear- and anxiety-
related responses (e.g., arousal, avoidance, etc.) [64]. These structures, together
with the vmPFC (and possibly portions of the sgACC; Fig. 2.4) are involved in the
degree to which anxiety- and fear-related responses are expressed or inhibited.

Insular Cortex

The insular cortex (Fig. 2.5) is believed to play a key role in interoception—the per-
ception of the internal state of the body from information conveyed to the cortex by
afferent pathways from the body via brainstem and thalamic intermediaries [65–68].
Abnormalities in the perception of interoceptive information are believed to contrib-
ute to symptoms of multiple psychiatric conditions including anxiety disorders [69–

Fig. 2.3 Sagittal rendering of the rostral anterior cingulate cortex
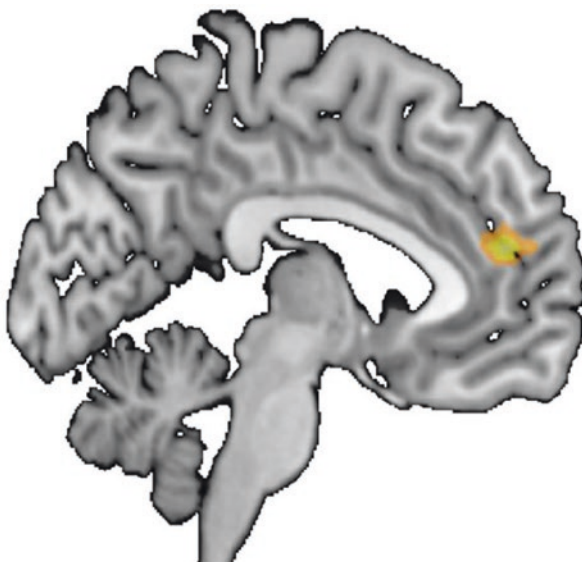
Fig. 2.4 Sagittal rendering of the subgenual anterior cingulate cortex
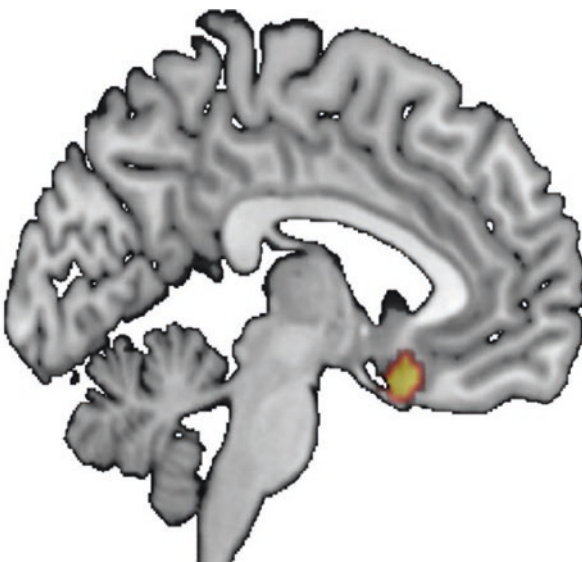
71]. The insula shows a posteroanterior gradient in successive stages of interoceptive processing [66, 68]. Posterior regions receive interoceptive information from ascending inputs, middle regions integrate this information with other sensory modalities, and such integrated information is then re-represented in the anterior insula where it contributes to subjective feeling states in concert with prefrontal areas [66, 68]. Laboratory studies have shown insula activation during a wide array of processes in addition to interoception such as emotional and self-awareness, empathy and
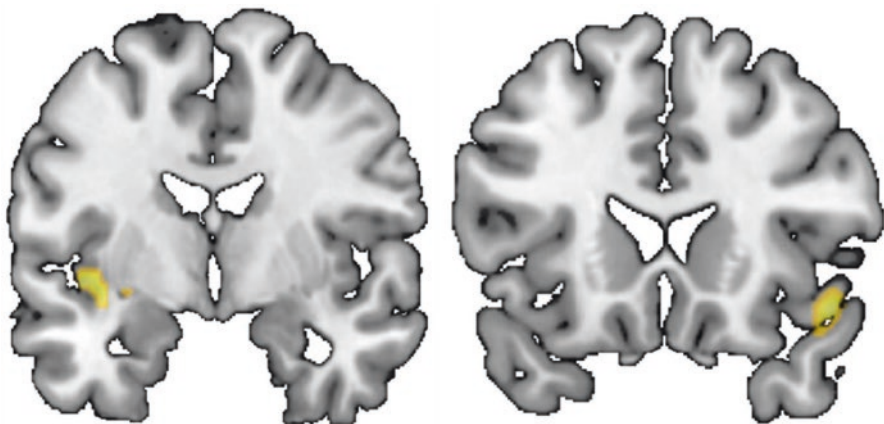
Fig. 2.5 Coronal rendering of the right and left insular cortex

empathic pain, and time perception [66, 72–74]. Of clinical interest, the insula is implicated in threat anticipation and situational uncertainty [22, 66]. Studies with healthy individuals have demonstrated greater activation of the insula upon the presentation of an aversive stimulus when the stimulus followed an uncertain cue, such that at times the cue was followed by a neutral stimulus and at times was followed by the aversive stimulus [75]. Interestingly, almost 75% of this sample overestimated the presence of an aversive stimulus following the uncertain cue, and insular activation was positively correlated with this estimate. Considering its role in threat detection, it should come to no surprise that activity in the insular cortex is highly correlated with amygdala and rACC activation, such that rACC activation caused by anticipation of an aversive stimulus was negatively correlated with activation of the insula and amygdala [22, 66, 75]. In fMRI, comparisons between anxiety-disordered and healthy individuals presented with [1] or anticipating [76–79] aversive stimuli, greater insula activation in anxious individuals is ubiquitously seen. Researchers hypothesize that the insula may play a role in pathological anxiety by overestimating the frequency of aversive outcomes in ambiguous situations or by incorrectly categorizing the situation as being predictive of an aversive outcome due to hyperactivation of the amygdala [22, 80]. Notably, in PPI studies, co-activation of the insula and dACC is often seen during processing of threat or pain [81], and, in rsFC studies, the insula appears as a key node of the salience network [47].

Hippocampus

The hippocampus (Fig. 2.6) is most commonly known for its role in memory formation as seen in the famous case of the patient H.M., who was no longer able to encode new declarative memories but who had perfect cognitive functioning otherwise, including encoding of new procedural memories, following a lobectomy that

Fig. 2.6 Coronal rendering of the right and left hippocampus
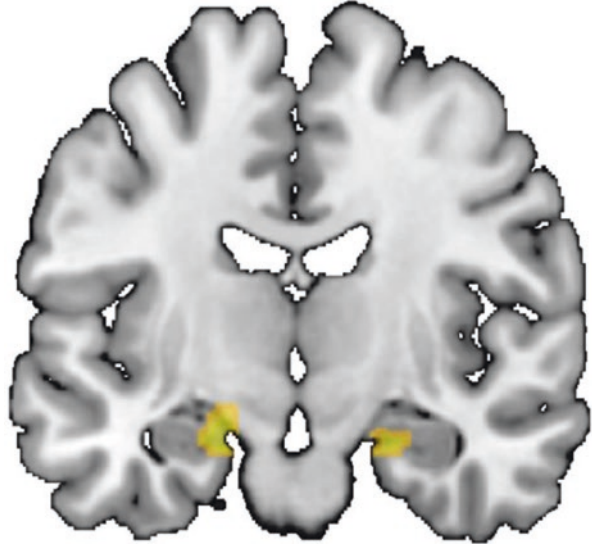
removed a sizable portion of his hippocampus. A key memory-related function of the hippocampus, which may become impaired in anxiety and anxiety-related disorders such as PTSD, is the provision of contextual information to disambiguate whether a stimulus that could represent danger in fact does so [11, 82]. However, the hippocampus is also involved in autonomic functions and is part of the negative-feedback loop of the hypothalamic-adrenal-pituitary (HPA) axis stress-response pathway [3, 83]. Functionally, the hippocampus can be split into two regions: (1) the dorsal hippocampus, which has been historically implicated in the processing and encoding of memories and learning, and (2) the ventral hippocampus, which is implicated in anxiety and stress responses [84]. Although some have argued in favor of the functional dichotomy of the hippocampus with findings that lesions to the ventral hippocampus lead to inhibition of anxiety response (i.e., freezing) in contextual conditioned-freezing paradigms, Bannerman et al. [84] propose that the ventral hippocampus' extensive and unique role in projection to the prefrontal cortex may be the pathway through which the hippocampus is able to regulate encoding of aversive and threatening memories [85, 86].

Inferior Prefrontal Cortex (PFC)

Broadly, the prefrontal cortex is involved in the processing and implementation of executive functions such as planning, decision-making, personality expression, behavioral inhibition, and emotion regulation. Here, we will take a closer look into the role of the inferior PFC in response inhibition and emotion regulation. Early research on the PFC demonstrated greater activation of the right inferior PFC (rIFC)

during the inhibition phase of the go/no-go task (where participants are asked to inhibit a prepotent response following a seldom-occurring cue) in healthy adults [87, 88]. Further evidence in lesion studies demonstrate that damage to the right inferior PFC is associated with poorer no-go trial performance in both humans and primates [89]. Decreased activation in the rIFC may be the underlying cause for response-inhibition difficulties in persons with attention-deficit hyperactivity disorder (ADHD) who demonstrate both poorer inhibition on no-go trials and decreased right, inferior PFC activation [87]. Subsequently, the rIFG has been implicated in domain-general inhibition (e.g., of action, cognition, emotion) [87, 88, 90, 91], and impairment of its inhibitory function has been linked with anxiety-related syndromes such as posttraumatic stress disorder (PTSD) [92, 93]. Notably, to engage higher-level emotion-regulatory processes such as cognitive reappraisal, the lateral PFC may recruit more primitive paralimbic regions along with their associated functions such as fear extinction [94].

Ventromedial Prefrontal Cortex (vmPFC)

The vmPFC (Fig. 2.7) is often implicated in neuroimaging studies of anxiety disorders [63] most often suggesting that the vmPFC suppresses negative affect through the inhibition of amygdala activation [59, 95–97]. For example, studies have demonstrated decreased activity in the vmPFC during trauma reminders as well as fear-conditioning paradigms with PTSD patients compared to trauma-exposed controls [97–100]. However, there also exist controversies. In a lesion study with war veterans which suggested that veterans with damage to the vmPFC were actually less

Fig. 2.7 Sagittal rendering of the left vmPFC
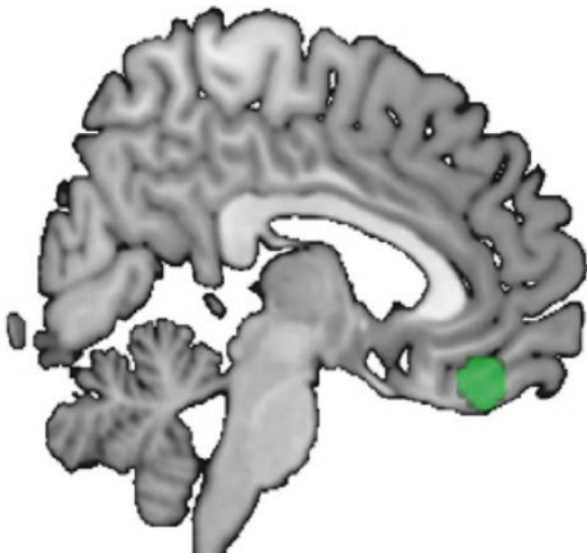
likely to develop PTSD than those with intact vmPFC. [63, 101] note that several other studies have found a negative relationship between vmPFC activity and reported anxiety symptoms. Therefore, Myers-Schulz et al. [63] propose that the vmPFC as a whole is involved in the general modulation of amygdala activity, including both inhibitory and excitatory functions, and that each of these is modulated by subregions of the vmPFC: the posterior vmPFC (corresponding to the sgACC) and the perigenual PFC. Together, these studies suggest that the perigenual area of the vmPFC may be modulating positive affect, while the posterior vmPFC/sgACC may be modulating negative affect [63].

Integrative Models

As one can see, deviances from each of these structures' non-pathological, and often evolutionarily adaptive, functions may lead to exacerbated fear encoding, anxiety, and excitatory responses. Basic research using animal models in combination with fear-acquisition paradigms have been able to identify some of the macro-circuitry involved in anxiety disorders. Such models begin to elucidate the pathways associated with threat interpretation, evaluation, and response loops. The literature suggests that initial threat interpretation starts in the amygdala, projects to the BNST, and then follows to the hippocampus and medial prefrontal cortex (mPFC [102]). In this pathway, the amygdala's major nucleus of information processing (basolateral amygdala or BLA) not only assigns emotional valance to a stimulus but also creates connections indicating the predictive value of a stimulus (Fig. 2.8 [102, 103]). In other words, this step determines whether neutral stimuli predict positive or negative outcomes, in addition to evaluating the valence of the outcome itself. The assigned valence to emotional content is then processed in the mPFC and hippocampus, which determine whether or not it is worthy of enhanced vigilance based on previous experiences, and then projects the signal back to the BNST and the amygdala [102]. An interesting concomitant to more extended processing networks LeDoux's [104] concept of a "high" and "low" road to fear responses whereby sensory cues indicative of danger can bypass more extensive processing in sensory cortices and instead trigger motor responses via a low road proceeding from the sensory thalamus directly to the BLA and, thence, via the central nucleus (CeA, the main amygdala output nucleus) to rapid defensive responses mediated by the hypothalamus, autonomic nervous system, and brainstem. In addition to sensory cues alone, such responses in the amygdala can be modified by the evaluation of contextual information in the hippocampus [104]. Considering how these structures are some of the brain's main information-processing and relay centers, it is no surprise that changes in one region may trigger a cascade of events that go on to cause neurochemical and anatomical deviances. Although each anxiety disorder may not implicate all of these brain regions due to distinct features of their behavioral and cognitive manifestations, these structures serve as the main foundation for fear acquisition, extinction, and maintenance. Below, we will explore current hypotheses
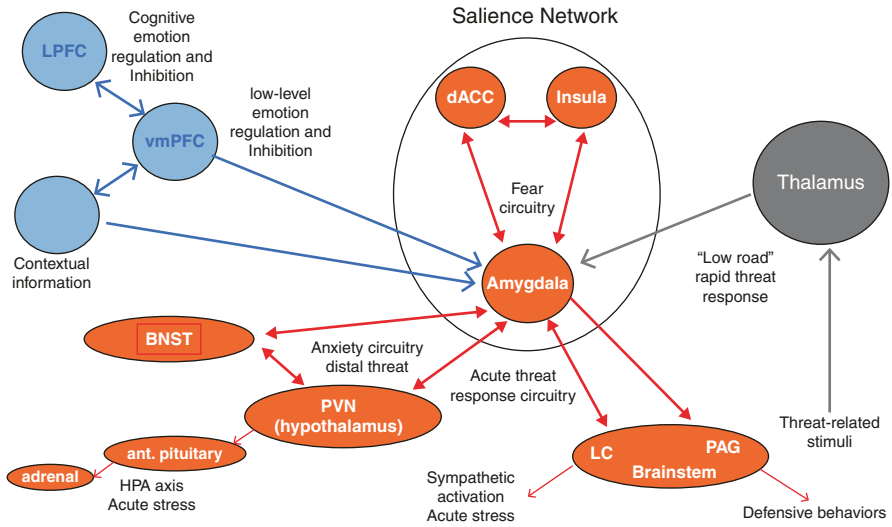
Fig. 2.8 Representative structures engaged in normal and pathological anxiety and the behavioral responses subserved. Connectivity illustrated is highly simplified and does not show extensive interconnections among structures depicted (e.g., BNST and vmPFC) and not depicted (e.g., sgACC, ventral striatum). BNST bed nucleus of the stria terminalis, dACC dorsal anterior cingulate cortex, HPA hypothalamic-pituitary-adrenal, LC locus coeruleus, LPFC-lateral prefrontal cortex, PAG periaqueductal gray, PVN paraventricular nucleus, vmPFC ventromedial prefrontal cortex, Red structures: fear and anxiety promoting. Blue structures: fear and anxiety regulatory

for the neural mechanisms behind specific phobia, generalized anxiety disorders (GAD), social anxiety disorder (SAD), panic disorder (PD), and posttraumatic stress disorder (PTSD).

Neural Mechanisms Implicated in Specific Anxiety Disorders

Specific Phobia

Specific phobia is perhaps one of the disorders most closely modeled by the fear paradigm due to having a clearly identified stimulus and a fear response that dissipates upon the removal of the stimulus. There is also a clearer body of literature detailing the neural pathway of specific phobias than that of other anxiety disorders. Studies exploring the neurocircuitry of specific phobia have reported increased activation and connectivity of the amygdala, with the degree of amygdala hyperactivation predicting symptom severity [2, 3, 105]. However, findings are mixed, and results consistently show hyperactivation of other fear-processing and fear-response regions such as the insula and dACC suggesting an overall exacerbated fear response throughout the salience network in individuals with specific phobia [2, 3]. Furthermore,

other studies have also shown decreased activation of the vmPFC when participants were presented with phobic stimuli, suggesting less regulation of the amygdala by the PFC [106]. Cognitive behavioral therapy as well as the habituation and extinction resulting from exposure to phobic stimuli has been demonstrated to decrease activation of the dACC and the insula in individuals with specific phobia, but not to increase activation of the vmPFC [3]. These results suggest that there is a greater dysfunction in the threat-processing and threat-response regions than in emotion-regulatory regions for individuals with specific phobia. It is important to note, however, that neural activation in individuals with specific phobia will differ slightly depending on the phobic stimuli. For example, Hilbert et al. [107] found increased white matter volume in the left PFC in individuals with dental phobia, but not in individuals with snake phobia. An interesting ongoing controversy is whether some of the most common phobic stimuli (e.g., spiders, snakes, heights) are "biologically prepared" or potentiated by brain mechanisms that evolved in response to environmental threats in ancestral humans [108, 109]. Like specific phobia, we also see unique patterns of activation in SAD, which are discussed next.

Social Anxiety Disorder (SAD)

The general pathophysiology of SAD is similar to that of other fear- and worry-driven disorders in that there is an abnormality in the threat interpretation, evaluation, and response circuits of the brain. However, as we mentioned in earlier sections, the disorder's hallmark feature of anxiety surrounding social situations leads to somewhat different activation patterns than those of strictly fear- or worry-driven disorders. SAD differs from other anxiety disorders as it encompasses worry, constant self-evaluation, and out-of-proportion fear reactions to specific stimuli [110]. Much like in GAD, SAD neurobiology has implicated abnormalities in emotion-regulation structures such as the amygdala, insula, ACC, hippocampus, and mPFC [111]. Uniquely, studies with SAD patients have demonstrated elevated activity in the fusiform gyrus' face area and occipital lobe when patients were presented with images of fearful faces (compared to healthy controls [112]). These findings suggest greater processing of social stimuli for SAD patients than for healthy controls and are convergent with literature verifying that the fusiform face area is dedicated exclusively to the processing of facial features and face-like arrangements [113]. The fusiform face area also had greater connectivity to the amygdala in tasks where participants were shown fearful faces, but not in tasks involving symptom provocation (e.g., anticipation of public speaking) [112, 114–117]. Further studies have demonstrated greater rsFC of the amygdala with the rACC and insula [3, 117]. Although some studies report decreased activation in the mPFC and vmPFC in individuals with SAD, which would be consistent with findings suggesting decreased top-down regulation of the amygdala by these prefrontal structures, other studies have observed increased activation and connectivity between the amygdala and these regions [2, 3]. According to Shin and Liberzon [3], the heterogeneity in the

results could be explained by a study that found delayed responses of the mPFC in SAD during the presentation of fearful faces. Nonetheless, cognitive behavioral interventions targeting cognitive reframing, or reappraisal, of negative emotions and events have demonstrated decreased activation of the amygdala following treatment [118]. These studies have also demonstrated that differences in symptom severity (namely, decreases) were negatively correlated with connectivity between the amygdala and inferior PFC regions (i.e., vmPFC and ventrolateral PFC) [116, 118]. The discordance across these results could be due to the diverse functions associated with the different subregions of the vmPFC in threat processing. Further studies are needed in order to determine the exact connectivity between the prefrontal cortex and the amygdala in SAD.

Generalized Anxiety Disorder (GAD)

There is somewhat of a dearth of literature on the neural pathways of GAD, despite its high lifetime prevalence (5%) around the world [119, 120]. Currently, the literature proposes two models for the potential pathophysiology of GAD. The first is the "emotional dysregulation model," which proposes that individuals with GAD turn to worry due to difficulties with emotion regulation [121]. Although there is competing evidence, a large portion of studies supporting this model report hypoactivation of the mPFC and ACC in individuals diagnosed with GAD, suggesting that there may be a lack top-down regulation of amygdala activity. For example, an rsFC study showed reduced connectivity between the amygdala and frontal regions such as the dorsolateral PFC [122]. The other is the "conditioned fear generalization theory" which, as Mochcovitch et al. [121] point out, is only supported by a handful of studies. This theory postulates that conditioned fear is overgeneralized to non-threatening, perceptually similar cues, increasing the probability that those events will also trigger fear- and anxiety-type responses [123]. Greenberg [124] found that healthy individuals seemed to recruit the insula, rACC, vmPFC, and amygdala during a fear generalization task, where we see increased activity in the insula, rACC, and amygdala activation during initial stimuli presentation which decreases as the brain determines the threat is specific to one stimulus. As this specificity occurs, we see increases in vmPFC activation and decreases in the aforementioned areas, which further supports the theory that vmPFC function is involved in amygdala regulation. When the same task was conducted with GAD participants, there appeared to be a lack of increased vmPFC activation during generalization and prolonged activation of fear evaluation, interpretation, and response loops (e.g., amygdala, dACC, and insula [124]). Although the two models propose different paths through which symptoms may develop and be maintained in GAD, they both provide compelling evidence for a deficit in regulation of responses to aversive stimuli. These findings in functional connectivity are congruent with other findings suggesting generally decreases in activation of emotion-modulation regions in GAD (i.e., hippocampus, mPFC, rACC) and increases in activation of slow- and prolonged-onset fear-response

structures such as the BNST [2, 125]. In GAD, we see decreased connectivity between the amygdala and the mPFC, as well as decreased connectivity among the inferior PFC, amygdala, and rACC [126]. A recent review found that PFC hypoactivation with abnormal PFC-amygdala connectivity was the most typical finding in fMRI studies of GAD [121]. Furthermore, some studies have also found increased connectivity between the insula and the amygdala in GAD patients, suggesting hyperactivity of the salience network [2]. However, in another rsFC study, amygdala connectivity was reduced to areas of the salience network including the anterior insula and dorsal anterior cingulate cortex (dACC) but increased to areas of the central executive network—a finding interpreted as a compensatory effort to self-regulate anxiety [127]. Despite their variability, these findings together suggest that increasing emotion regulation in GAD patients may be an effective treatment target. Fortunately, studies that collected rsFC data pre- and post-CBT treatment for GAD have demonstrated not only attenuated activity of the amygdala, rACC, and mPFC during exposure to negative stimuli, but also increased activation of those areas during presentation of positively valanced stimuli (e.g., happy faces), as well as increased connectivity between the amygdala and insula [128].

Panic Disorder (PD)

Panic disorder is marked by sudden or unexpected panic attacks, along with frequent worrying about future attacks or changes in behavior related to the attacks including agoraphobia [110]. Current literature supports a pathophysiological model of PD suggesting hyperactivation of the amygdala, hippocampus, thalamus, and brainstem structures [129]. In agreement with this model, studies have demonstrated greater activation in fear network regions such as the striatum and the dACC [57, 130]. Heightened interoceptive sensitivity has also been widely documented in PD [131–133], while interoceptive conditioning is implicated in its etiology [134] and interoceptive exposure therapy is employed in its treatment [135]. Accordingly, in persons with PD, there are reports of heightened reactivity of insular cortex to emotional tasks [136, 137] as well as reduced numbers of insula benzodiazepine binding sites [138]. Although the exact function of the dACC in PD has yet to be determined, case studies reporting both immediate and delayed onset of panic attacks following surgical removal of the dACC in humans suggest it plays a key role in the disorder [139]. Unlike other anxiety disorders, there have been inconsistent findings regarding amygdala activation in PD patients, with studies suggesting both hypo- and hyperactivation of this structure [137, 140–142]. Despite the lack of evidence for amygdala hyperactivation, several structural MRI studies have found volumetric deficits in the amygdala of individuals with PD [141, 143–145]. Gorman et al.'s [129] model of PD also points to the role of the hippocampus in contextualizing fearful situations. Generally, phobic avoidance arises from people with PD associating their fearful state (a panic attack) with the situation or scenes that were present at the time of their panic. Even with successful treatment, patients may still avoid situations contextu-

ally similar to those in which they had a panic attack due to this conditioning. Since the hippocampus is necessary for contextualization, Gorman and colleagues suggested that the hippocampus may be a treatment target for deconditioning contextual fear learning. A review by Shin and Liberzon [3] has also implicated abnormal hippocampal activity within PD. While there is little evidence from fMRI research, structural MRI studies have found a decrease in hippocampal volumes and density of persons with panic disorder, suggesting decreased consolidation of extinction and generalization memories for these individuals [141, 144, 145].

Posttraumatic Stress Disorder (PTSD)

Although not a perfect model, fear-conditioning studies have also been used to study PTSD and its neurocircuitry (see [146]). In general, it appears that individuals with PTSD are better at fear learning (conditioning) and worse at learning extinction and later recalling these extinction memories due to abnormalities in their fear network [147, 148]. Imaging studies of PTSD tend to report hyperactivation in the amygdala both at rest [149, 150] and during task-based experiments [99, 151] (reviewed in [152]), which may lead to an exaggerated fear response. Individuals with PTSD demonstrate exacerbated activation of the amygdala and dACC as well as increased skin conductance response (SCR), suggesting increased processing of threatening stimuli [153, 154]. Furthermore, several imaging studies have reported hypoactivation of the mPFC, vmPFC, and rACC in individuals with PTSD, suggesting deficits in regulation of fear-processing structures, e.g., amygdala, insula, and dACC, as seen in GAD, SAD, and PD [155, 156] (reviewed in [3]). Additionally, the vmPFC and hippocampus are important for fear-conditioning generalization. Studies with healthy controls demonstrate activation in both regions when subjects were presented with stimuli that only resembled the conditioned stimulus and successfully generalized previous extinction learning [157]. Both increases and decreases in hippocampal activity have been correlated with PTSD severity (reviewed in [3] and [2]). While activation patterns are unclear, abnormal hippocampal function may play a role in the tendency of PTSD patients to generalize their fear response to situations and contexts that differ from the trauma. Convergent with this hypothesis, studies have shown decreased hippocampal and vmPFC volumes in patients with PTSD [158–163]. Some researchers even suggest that smaller hippocampal volume may be a precursor to PTSD development. In a twin study of combat-exposed individuals, the twin sibling of veterans with PTSD had smaller hippocampal volume than that of twins of veterans without PTSD, independent of trauma exposure [164] reviewed in [100]. Sleep deficiencies are also a potential precursor and target for PTSD. Objective and subjective sleep abnormalities, including subjective insomnia reports, either preceding or following traumatic experiences, predict later development of PTSD (reviewed in [165–167]). Such findings suggest that sleep disturbances may be a precursor to, in addition to a consequence of, PTSD development and may play a key role in the etiology of this disorder [165–174]

Conclusion

In summary, the pathophysiology of anxiety disorders is marked by abnormalities in emotion-processing structures, particularly the amygdala, BNST, rACC, and insula as well as in emotion-regulation structures such as the vmPFC, dACC, mPFC, and hippocampus. Although studies suggest that fear-driven disorders (e.g., SAD and specific phobia) have greater deficits in emotion-processing structures, while worry-driven disorders (e.g., GAD and PD) are categorized by deficits in emotion-regulation pathways, disturbances occur across all points of the threat interpretation, evaluation, and response loops which is more clearly defined in the neurocircuitry of PTSD. Further studies and greater homogeneity across study methodology are needed to advance greater understanding of these disorders and avoid potential misunderstandings in anatomical specificity. Studies exploring the effects of well-validated interventions for anxiety disorders may be of particular benefit in untangling the connection between behavior, cognition, and functional neuroimaging for the development of future treatment targets.

References

1. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007;164(10):1476–88.
2. Duval ER, Javanbakht A, Liberzon I. Neural circuits in anxiety and stress disorders: a focused review. Ther Clin Risk Manag. 2015;11:115–26. https://doi.org/10.2147/TCRM.S48528.
3. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology. 2010;35(1):169–91. https://doi.org/10.1038/npp.2009.83.
4. Rauch SL, Shin LM, Wright CI. Neuroimaging studies of amygdala function in anxiety disorders. Ann N Y Acad Sci. 2003;985(1):389–410.
5. Raichle ME. The restless brain. Brain Connect. 2011;1(1):3–12. https://doi.org/10.1089/brain.2011.0019.
6. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex. 2009;19(1):72–8. https://doi.org/10.1093/cercor/bhn059.
7. Fox MD, Greicius M. Clinical applications of resting state functional connectivity. Front Syst Neurosci. 2010;4:19.
8. Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: ten years of progress. Annu Rev Psychol. 2012;63:129–51. https://doi.org/10.1146/annurev.psych.121208.131631.
9. Lonsdorf TB, Menz MM, Andreatta M, Fullana MA, Golkar A, Haaker J, et al. Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. Neurosci Biobehav Rev. 2017;77:247–85. https://doi.org/10.1016/j.neubiorev.2017.02.026.
10. Lonsdorf TB, Merz CJ. More than just noise: Inter-individual differences in fear acquisition, extinction and return of fear in humans – Biological, experiential, temperamental factors, and methodological pitfalls. Neurosci Biobehav Rev. 2017;80:703–28. https://doi.org/10.1016/j.neubiorev.2017.07.007.

11. Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology. 2008;33(1):56–72.
12. Hermans D, Craske MG, Mineka S, Lovibond PF. Extinction in human fear conditioning. Biol Psychiatry. 2006;60(4):361–8.
13. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behav Res Ther. 2008;46(1):5–27.
14. McNally RJ. Mechanisms of exposure therapy: how neuroscience can improve psychological treatments for anxiety disorders. Clin Psychol Rev. 2007;27(6):750–9.
15. Beckers T, Krypotos A-M, Boddez Y, Effting M, Kindt M. What's wrong with fear conditioning? Biol Psychol. 2013;92(1):90–6.
16. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry. 2007;62(5):446–54.
17. Quirk GJ, Garcia R, Gonzalez-Lima F. Prefrontal mechanisms in extinction of conditioned fear. Biol Psychiatry. 2006;60(4):337–43.
18. Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA. 2012;307(20):2169–76. https://doi.org/10.1001/jama.2012.3418.
19. Duits P, Cath DC, Lissek S, Hox JJ, Hamm AO, Engelhard IM, et al. Updated meta-analysis of classical fear conditioning in the anxiety disorders. Depress Anxiety. 2015;32(4):239–53. https://doi.org/10.1002/da.22353.
20. Milad MR, Rauch SL. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn Sci. 2012;16(1):43–51. https://doi.org/10.1016/j.tics.2011.11.003.
21. Liberzon I, Martis B. Neuroimaging studies of emotional responses in PTSD. Ann N Y Acad Sci. 2006;1071:87–109. https://doi.org/10.1196/annals.1364.009.
22. Taylor JM, Whalen PJ. Neuroimaging and anxiety: The neural substrates of pathological and non-pathological anxiety. Curr Psychiatry Rep. 2015;17(6):49.
23. Abelson JL, Khan S, Liberzon I, Young EA. HPA axis activity in patients with panic disorder: review and synthesis of four studies. Depress Anxiety. 2007;24(1):66–76.
24. Knight DC, Nguyen HT, Bandettini PA. The role of the human amygdala in the production of conditioned fear responses. NeuroImage. 2005;26(4):1193–200.
25. Hariri AR, Holmes A. Genetics of emotional regulation: the role of the serotonin transporter in neural function. Trends Cogn Sci. 2006;10(4):182–91. https://doi.org/10.1016/j.tics.2006.02.011.
26. Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, et al. A susceptibility gene for affective disorders and the response of the human amygdala. Arch Gen Psychiatry. 2005;62(2):146–52. https://doi.org/10.1001/archpsyc.62.2.146.
27. Furmark T, Tillfors M, Garpenstrand H, Marteinsdottir I, Langstrom B, Oreland L, et al. Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. Neurosci Lett. 2004;362(3):189–92.
28. Drabant EM, Ramel W, Edge MD, Hyde LW, Kuo JR, Goldin PR, et al. Neural mechanisms underlying 5-HTTLPR-related sensitivity to acute stress. Am J Psychiatry. 2012;169(4):397–405.
29. Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev. 2000;24(4):417–63.
30. Casey B, Jones RM, Somerville LH. Braking and Accelerating of the Adolescent Brain. J Res Adolesc. 2011;21(1):21–33. https://doi.org/10.1111/j.1532-7795.2010.00712.x.
31. Casey B, Ruberry EJ, Libby V, Glatt CE, Hare T, Soliman F, et al. Transitional and translational studies of risk for anxiety. Depress Anxiety. 2011;28(1):18–28.
32. Bishop SJ, Duncan J, Lawrence AD. State anxiety modulation of the amygdala response to unattended threat-related stimuli. J Neurosci. 2004;24(46):10364–8.
33. Davis M, Walker DL, Miles L, Grillon C. Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. Neuropsychopharmacology. 2010;35(1):105–35. https://doi.org/10.1038/npp.2009.109.

34. Walker DL, Ressler KJ, Lu KT, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci. 2002;22(6):2343–51.

35. Lebow MA, Chen A. Overshadowed by the amygdala: the bed nucleus of the stria terminalis emerges as key to psychiatric disorders. Mol Psychiatry. 2016;21(4):450–63. https://doi.org/10.1038/mp.2016.1.

36. Walker DL, Toufexis DJ, Davis M. Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. Eur J Pharmacol. 2003;463(1-3):199–216.

37. Kazama AM, Heuer E, Davis M, Bachevalier J. Effects of neonatal amygdala lesions on fear learning, conditioned inhibition, and extinction in adult macaques. Behav Neurosci. 2012;126(3):392–403. https://doi.org/10.1037/a0028241.

38. Poulos AM, Ponnusamy R, Dong HW, Fanselow MS. Compensation in the neural circuitry of fear conditioning awakens learning circuits in the bed nuclei of the stria terminalis. Proc Natl Acad Sci U S A. 2010;107(33):14881–6. https://doi.org/10.1073/pnas.1005754107.

39. Lockwood PL, Wittmann MK. Ventral anterior cingulate cortex and social decision-making. Neurosci Biobehav Rev. 2018;92:187–91. https://doi.org/10.1016/j.neubiorev.2018.05.030.

40. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain. 1995;118(Pt 1):279–306.

41. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci. 2000;4(6):215–22.

42. Marusak H, Thomason M, Peters C, Zundel C, Elrahal F, Rabinak C. You say 'prefrontal cortex' and I say 'anterior cingulate': meta-analysis of spatial overlap in amygdala-to-prefrontal connectivity and internalizing symptomology. Transl Psychiatry. 2016;6(11):e944.

43. Lieberman MD, Eisenberger NI. The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference. Proc Natl Acad Sci U S A. 2015;112(49):15250–5. https://doi.org/10.1073/pnas.1515083112.

44. Cheng DT, Knight DC, Smith CN, Helmstetter FJ. Human amygdala activity during the expression of fear responses. Behav Neurosci. 2006;120(6):1187.

45. Cheng DT, Knight DC, Smith CN, Stein EA, Helmstetter FJ. Functional MRI of human amygdala activity during Pavlovian fear conditioning: stimulus processing versus response expression. Behav Neurosci. 2003;117(1):3.

46. Milad MR, Quirk GJ, Pitman RK, Orr SP, Fischl B, Rauch SL. A role for the human dorsal anterior cingulate cortex in fear expression. Biol Psychiatry. 2007;62(10):1191–4.

47. Chen T, Cai W, Ryali S, Supekar K, Menon V. Distinct global brain dynamics and spatio-temporal organization of the salience network. PLoS Biol. 2016;14(6):e1002469. https://doi.org/10.1371/journal.pbio.1002469.

48. Critchley HD. Electrodermal responses: what happens in the brain. Neuroscientist. 2002;8(2):132–42.

49. Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, et al. The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. Biol Psychiatry. 1998;44(12):1219–28.

50. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry. 2008;13:833–57.

51. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron. 2006;51(6):871–82. https://doi.org/10.1016/j.neuron.2006.07.029.

52. Dodhia S, Hosanagar A, Fitzgerald DA, Labuschagne I, Wood AG, Nathan PJ, et al. Modulation of resting-state amygdala-frontal functional connectivity by oxytocin in generalized social anxiety disorder. Neuropsychopharmacology. 2014;39(9):2061–9. https://doi.org/10.1038/npp.2014.53.

53. Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology. 2011;36(1):183–206. https://doi.org/10.1038/npp.2010.166.

54. Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex. 2000;10(3):206–19.
55. Drevets WC, Savitz J, Trimble M. The subgenual anterior cingulate cortex in mood disorders. CNS Spectr. 2008;13(8):663–81.
56. Johansen-Berg H, Gutman DA, Behrens TE, Matthews PM, Rushworth MF, Katz E, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. Cereb Cortex. 2008;18(6):1374–83.
57. Tuescher O, Protopopescu X, Pan H, Cloitre M, Butler T, Goldstein M, et al. Differential activity of subgenual cingulate and brainstem in panic disorder and PTSD. J Anxiety Disord. 2011;25(2):251–7. https://doi.org/10.1016/j.janxdis.2010.09.010.
58. Haas BW, Omura K, Constable RT, Canli T. Emotional conflict and neuroticism: personality-dependent activation in the amygdala and subgenual anterior cingulate. Behav Neurosci. 2007;121(2):249–56. https://doi.org/10.1037/0735-7044.121.2.249.
59. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. Neuron. 2004;43(6):897–905.
60. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45(5):651–60.
61. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry. 2000;48(8):830–43.
62. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur Neuropsychopharmacol. 2002;12(6):527–44.
63. Myers-Schulz B, Koenigs M. Functional anatomy of ventromedial prefrontal cortex: implications for mood and anxiety disorders. Mol Psychiatry. 2012;17(2):132–41. https://doi.org/10.1038/mp.2011.88.
64. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci. 2011;15(2):85–93. https://doi.org/10.1016/j.tics.2010.11.004.
65. Craig AD. How do you feel? interoception: the sense of the physiological condition of the body. Nat Rev. 2002;3(8):655–66.
66. Craig AD. How do you feel – now? The anterior insula and human awareness. Nature reviews. 2009;10(1):59–70.
67. Craig AD. Significance of the insula for the evolution of human awareness of feelings from the body. Ann N Y Acad Sci. 2011;1225:72–82. https://doi.org/10.1111/j.1749-6632.2011.05990.x.
68. Namkung H, Kim SH, Sawa A. The insula: an underestimated brain area in clinical neuroscience, psychiatry, and neurology. Trends Neurosci. 2017;40(4):200–7. https://doi.org/10.1016/j.tins.2017.02.002.
69. Khalsa SS, Adolphs R, Cameron OG, Critchley HD, Davenport PW, Feinstein JS, et al. Interoception and mental health: a roadmap. Biol Psychiatry. 2018; https://doi.org/10.1016/j.bpsc.2017.12.004.
70. Murphy J, Brewer R, Catmur C, Bird G. Interoception and psychopathology: a developmental neuroscience perspective. Dev Cogn Neurosci. 2017;23:45–56. https://doi.org/10.1016/j.dcn.2016.12.006.
71. Seth AK, Friston KJ. Active interoceptive inference and the emotional brain. Philos Trans R Soc Lond Ser B Biol Sci. 2016;371(1708) https://doi.org/10.1098/rstb.2016.0007.
72. Bernhardt BC, Singer T. The neural basis of empathy. Annu Rev Neurosci. 2012;35:1–23. https://doi.org/10.1146/annurev-neuro-062111-150536.
73. Zaki J, Wager TD, Singer T, Keysers C, Gazzola V. The anatomy of suffering: understanding the relationship between nociceptive and empathic pain. Trends Cogn Sci. 2016;20(4):249–59. https://doi.org/10.1016/j.tics.2016.02.003.
74. Craig AD. How do you feel? an interoceptive moment with your neurobiological self. Princeton: Princeton University Press; 2016.
75. Sarinopoulos I, Grupe D, Mackiewicz K, Herrington J, Lor M, Steege E, et al. Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. Cereb Cortex. 2009;20(4):929–40.

76. Chua P, Krams M, Toni I, Passingham R, Dolan R. A functional anatomy of anticipatory anxiety. NeuroImage. 1999;9(6 Pt 1):563–71. https://doi.org/10.1006/nimg.1999.0407.

77. Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, et al. Dissociating pain from its anticipation in the human brain. Science. 1999;284(5422):1979–81.

78. Simmons A, Matthews SC, Stein MB, Paulus MP. Anticipation of emotionally aversive visual stimuli activates right insula. Neuroreport. 2004;15(14):2261–5.

79. Simmons A, Strigo I, Matthews SC, Paulus MP, Stein MB. Anticipation of aversive visual stimuli is associated with increased insula activation in anxiety-prone subjects. Biol Psychiatry. 2006;60(4):402–9. https://doi.org/10.1016/j.biopsych.2006.04.038.

80. Paulus MP. The role of neuroimaging for the diagnosis and treatment of anxiety disorders. Depress Anxiety. 2008;25(4):348–56.

81. Klumpp H, Angstadt M, Phan KL. Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. Biol Psychol. 2012;89(1):273–6. https://doi.org/10.1016/j.biopsycho.2011.10.010.

82. Ji J, Maren S. Hippocampal involvement in contextual modulation of fear extinction. Hippocampus. 2007;17(9):749–58.

83. Martin EI, Ressler KJ, Binder E, Nemeroff CBJPC. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. Psychiatr Clin. 2009;32(3):549–75.

84. Bannerman D, Rawlins J, McHugh S, Deacon R, Yee B, Bast T, et al. Regional dissociations within the hippocampus – memory and anxiety. Neurosci Biobehav Rev. 2004;28(3):273–83.

85. Richmond M, Yee B, Pouzet B, Veenman L, Rawlins J, Feldon J, et al. Dissociating context and space within the hippocampus: effects of complete, dorsal, and ventral excitotoxic hippocampal lesions on conditioned freezing and spatial learning. Behav Neurosci. 1999;113(6):1189.

86. Kjelstrup KG, Tuvnes FA, Steffenach H-A, Murison R, Moser EI, Moser M-B. Reduced fear expression after lesions of the ventral hippocampus. Proc Natl Acad Sci. 2002;99(16):10825–30.

87. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci. 2004;8(4):170–7.

88. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci. 2014;18(4):177–85. https://doi.org/10.1016/j.tics.2013.12.003.

89. Iversen SD, Mishkin M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Exp Brain Res. 1970;11(4):376–86.

90. Aron AR, Robbins TW, Poldrack RA. Right inferior frontal cortex: addressing the rebuttals. Front Hum Neurosci. 2014;8:905. https://doi.org/10.3389/fnhum.2014.00905.

91. Dillon DG, Pizzagalli DA. Inhibition of Action, Thought, and Emotion: A Selective Neurobiological Review. Appl Prev Psychol. 2007;12(3):99–114.

92. van Rooij SJ, Rademaker AR, Kennis M, Vink M, Kahn RS, Geuze E. Impaired right inferior frontal gyrus response to contextual cues in male veterans with PTSD during response inhibition. J Psychiatry Neurosci. 2014;39(5):330–8.

93. Falconer E, Bryant R, Felmingham KL, Kemp AH, Gordon E, Peduto A, et al. The neural networks of inhibitory control in posttraumatic stress disorder. J Psychiatry Neurosci. 2008;33(5):413–22.

94. Delgado MR, Nearing KI, Ledoux JE, Phelps EA. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron. 2008;59(5):829–38.

95. Milad MR, Rauch SL. The role of the orbitofrontal cortex in anxiety disorders. Ann N Y Acad Sci. 2007;1121(1):546–61.

96. Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychol. 2006;73(1):61–71.

97. Jovanovic T, Ressler KJ. How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. Am J Psychiatry. 2010;167(6):648–62. https://doi.org/10.1176/appi.ajp.2009.09071074.

98. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present, and future. Biol Psychiatry. 2006;60(4):376–82.

99. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009;66(12):1075–82. https://doi.org/10.1016/j.biopsych.2009.06.026.

100. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. Nature reviews. 2012;13(11):769–87. https://doi.org/10.1038/nrn3339.

101. Koenigs M, Huey ED, Calamia M, Raymont V, Tranel D, Grafman J. Distinct regions of prefrontal cortex mediate resistance and vulnerability to depression. J Neurosci. 2008;28(47):12341–8.

102. Calhoon GG, Tye KM. Resolving the neural circuits of anxiety. Nat Neurosci. 2015;18(10):1394.

103. McDonald AJ. Cortical pathways to the mammalian amygdala. Prog Neurobiol. 1998;55(3):257–332.

104. LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23:155–84. https://doi.org/10.1146/annurev.neuro.23.1.155.

105. Lipka J, Miltner WH, Straube T. Vigilance for threat interacts with amygdala responses to subliminal threat cues in specific phobia. Biol Psychiatry. 2011;70(5):472–8. https://doi.org/10.1016/j.biopsych.2011.04.005.

106. Killgore WD, Britton JC, Schwab ZJ, Price LM, Weiner MR, Gold AL, et al. Cortico-limbic responses to masked affective faces across PTSD, panic disorder, and specific phobia. Depress Anxiety. 2014;31(2):150–9.

107. Hilbert K, Pine DS, Muehlhan M, Lueken U, Steudte-Schmiedgen S, Beesdo-Baum K. Gray and white matter volume abnormalities in generalized anxiety disorder by categorical and dimensional characterization. Psychiatry Res. 2015;234(3):314–20. https://doi.org/10.1016/j.pscychresns.2015.10.009.

108. Seligman MEP. Phobias and preparedness. Behav Ther. 1971;2:307–20.

109. Ohman A, Mineka S. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychol Rev. 2001;108(3):483–522.

110. APA. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.

111. Hattingh CJ, Ipser J, Tromp S, Syal S, Lochner C, SJB B, et al. Functional magnetic resonance imaging during emotion recognition in social anxiety disorder: an activation likelihood meta-analysis. Front Hum Neurosci. 2013;6:347.

112. Frick A, Howner K, Fischer H, Kristiansson M, Furmark T. Altered fusiform connectivity during processing of fearful faces in social anxiety disorder. Transl Psychiatry. 2013;3:e312. https://doi.org/10.1038/tp.2013.85.

113. Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci. 1997;17(11):4302–11.

114. Tillfors M, Furmark T, Marteinsdottir I, Fischer H, Pissiota A, Langstrom B, et al. Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a PET study. Am J Psychiatry. 2001;158(8):1220–6.

115. Lorberbaum JP, Kose S, Johnson MR, Arana GW, Sullivan LK, Hamner MB, et al. Neural correlates of speech anticipatory anxiety in generalized social phobia. Neuroreport. 2004;15(18):2701–5.

116. Danti S, Ricciardi E, Gentili C, Gobbini MI, Pietrini P, Guazzelli M. Is social phobia a "mis-communication" disorder? brain functional connectivity during face perception differs between patients with social phobia and healthy control subjects. Front Syst Neurosci. 2010;4:152. https://doi.org/10.3389/fnsys.2010.00152.

117. Klumpp H, Fitzgerald JM. Neuroimaging predictors and mechanisms of treatment response in social anxiety disorder: an overview of the Amygdala. Curr Psychiatry Rep. 2018;20(10):89. https://doi.org/10.1007/s11920-018-0948-1.

118. Young KS, Burklund LJ, Torre JB, Saxbe D, Lieberman MD, Craske MG. Treatment for social anxiety disorder alters functional connectivity in emotion regulation neu-

ral circuitry. Psychiatry Res Neuroimaging. 2017;261:44–51. https://doi.org/10.1016/j.pscychresns.2017.01.005.

119. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015;17(3):327–35.

120. Ruscio AM, Brown TA, Chiu WT, Sareen J, Stein MB, Kessler RC. Social fears and social phobia in the USA: results from the National Comorbidity Survey Replication. Psychol Med. 2008;38(1):15–28. https://doi.org/10.1017/S0033291707001699.

121. Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. J Affect Disord. 2014;167:336–42. https://doi.org/10.1016/j.jad.2014.06.041.

122. Liu WJ, Yin DZ, Cheng WH, Fan MX, You MN, Men WW, et al. Abnormal functional connectivity of the amygdala-based network in resting-state FMRI in adolescents with generalized anxiety disorder. Med Sci Monit. 2015;21:459–67. https://doi.org/10.12659/MSM.893373.

123. Lissek S. Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. Depress Anxiety. 2012;29(4):257–63. https://doi.org/10.1002/da.21922.

124. Greenberg T, Carlson JM, Cha J, Hajcak G, Mujica-Parodi LR. Neural reactivity tracks fear generalization gradients. Biol Psychol. 2013;92(1):2–8. https://doi.org/10.1016/j.biopsycho.2011.12.007.

125. Yassa MA, Hazlett RL, Stark CE, Hoehn-Saric R. Functional MRI of the amygdala and bed nucleus of the stria terminalis during conditions of uncertainty in generalized anxiety disorder. J Psychiatr Res. 2012;46(8):1045–52. https://doi.org/10.1016/j.jpsychires.2012.04.013.

126. Roy AK, Fudge JL, Kelly C, Perry JS, Daniele T, Carlisi C, et al. Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. J Am Acad Child Adolesc Psychiatry. 2013;52(3):290–9. e2. https://doi.org/10.1016/j.jaac.2012.12.010.

127. Etkin A, Prater KE, Schatzberg AF, Menon V, Greicius MD. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry. 2009;66(12):1361–72. https://doi.org/10.1001/archgenpsychiatry.2009.104.

128. Brooks SJ, Stein DJ. A systematic review of the neural bases of psychotherapy for anxiety and related disorders. Dialogues Clin Neurosci. 2015;17(3):261–79.

129. Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. Am J Psychiatry. 2000;157(4):493–505. https://doi.org/10.1176/appi.ajp.157.4.493.

130. de Carvalho MR, Dias GP, Cosci F, de-Melo-Neto VL, Bevilaqua MC, Gardino PF, et al. Current findings of fMRI in panic disorder: contributions for the fear neurocircuitry and CBT effects. Expert Rev Neurother. 2010;10(2):291–303. https://doi.org/10.1586/ern.09.161.

131. Yoris A, Esteves S, Couto B, Melloni M, Kichic R, Cetkovich M, et al. The roles of interoceptive sensitivity and metacognitive interoception in panic. Behav Brain Funct. 2015;11:14. https://doi.org/10.1186/s12993-015-0058-8.

132. Limmer J, Kornhuber J, Martin A. Panic and comorbid depression and their associations with stress reactivity, interoceptive awareness and interoceptive accuracy of various bioparameters. J Affect Disord. 2015;185:170–9. https://doi.org/10.1016/j.jad.2015.07.010.

133. Domschke K, Stevens S, Pfleiderer B, Gerlach AL. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. Clin Psychol Rev. 2010;30(1):1–11. https://doi.org/10.1016/j.cpr.2009.08.008.

134. De Cort K, Schroijen M, Hurlemann R, Claassen S, Hoogenhout J, Van den Bergh O, et al. Modeling the development of panic disorder with interoceptive conditioning. Eur Neuropsychopharmacol. 2017;27(1):59–69. https://doi.org/10.1016/j.euroneuro.2016.11.001.

135. Boettcher H, Brake CA, Barlow DH. Origins and outlook of interoceptive exposure. J Behav Ther Exp Psychiatry. 2016;53:41–51. https://doi.org/10.1016/j.jbtep.2015.10.009.

136. Gorka SM, Nelson BD, Phan KL, Shankman SA. Insula response to unpredictable and predictable aversiveness in individuals with panic disorder and comorbid depression. Biology of mood & anxiety disorders. 2014;4:9. https://doi.org/10.1186/2045-5380-4-9.

137. Sobanski T, Wagner G. Functional neuroanatomy in panic disorder: Status quo of the research. World J Psychiatry. 2017;7(1):12–33. https://doi.org/10.5498/wjp.v7.i1.12.

138. Cameron OG, Huang GC, Nichols T, Koeppe RA, Minoshima S, Rose D, et al. Reduced gamma-aminobutyric acid(A)-benzodiazepine binding sites in insular cortex of individuals with panic disorder. Arch Gen Psychiatry. 2007;64(7):793–800. https://doi.org/10.1001/archpsyc.64.7.793.

139. Shinoura N, Yamada R, Tabei Y, Otani R, Itoi C, Saito S, et al. Damage to the right dorsal anterior cingulate cortex induces panic disorder. J Affect Disord. 2011;133(3):569–72. https://doi.org/10.1016/j.jad.2011.04.029.

140. Dresler T, Guhn A, Tupak SV, Ehlis AC, Herrmann MJ, Fallgatter AJ, et al. Revise the revised? New dimensions of the neuroanatomical hypothesis of panic disorder. J Neural Transm (Vienna). 2013;120(1):3–29. https://doi.org/10.1007/s00702-012-0811-1.

141. Kim JE, Dager SR, Lyoo IK. The role of the amygdala in the pathophysiology of panic disorder: evidence from neuroimaging studies. Biology of mood & anxiety disorders. 2012;2:20. https://doi.org/10.1186/2045-5380-2-20.

142. Ottaviani C, Cevolani D, Nucifora V, Borlimi R, Agati R, Leonardi M, et al. Amygdala responses to masked and low spatial frequency fearful faces: a preliminary fMRI study in panic disorder. Psychiatry Res. 2012;203(2-3):159–65. https://doi.org/10.1016/j.pscychresns.2011.12.010.

143. Massana G, Serra-Grabulosa JM, Salgado-Pineda P, Gasto C, Junque C, Massana J, et al. Amygdalar atrophy in panic disorder patients detected by volumetric magnetic resonance imaging. NeuroImage. 2003;19(1):80–90.

144. Del Casale A, Serata D, Rapinesi C, Kotzalidis GD, Angeletti G, Tatarelli R, et al. Structural neuroimaging in patients with panic disorder: findings and limitations of recent studies. Psychiatr Danub. 2013;25(2):108–14.

145. Pannekoek JN, van der Werff SJ, Stein DJ, van der Wee NJ. Advances in the neuroimaging of panic disorder. Hum Psychopharmacol. 2013;28(6):608–11. https://doi.org/10.1002/hup.2349.

146. VanElzakker MB, Dahlgren MK, Davis FC, Dubois S, Shin LM. From Pavlov to PTSD: the extinction of conditioned fear in rodents, humans, and anxiety disorders. Neurobiol Learn Mem. 2014;113:3–18. https://doi.org/10.1016/j.nlm.2013.11.014.

147. VanElzakker MB. Posttraumatic Stress Disorder. In: Neuroscience in the 21st Century: From Basic to Clinical; 2016. p. 4055–84.

148. Garfinkel SN, Abelson JL, King AP, Sripada RK, Wang X, Gaines LM, et al. Impaired contextual modulation of memories in PTSD: an fMRI and psychophysiological study of extinction retention and fear renewal. J Neurosci. 2014;34(40):13435–43. https://doi.org/10.1523/JNEUROSCI.4287-13.2014.

149. Chung YA, Kim SH, Chung SK, Chae J-H, Yang DW, Sohn HS, et al. Alterations in cerebral perfusion in posttraumatic stress disorder patients without re-exposure to accident-related stimuli. Clin Neurophysiol. 2006;117(3):637–42.

150. Semple WE, Goyer PF, McCormick R, Donovan B, Muzic RF Jr, Rugle L, et al. Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. Psychiatry. 2000;63(1):65–74.

151. Bryant RA, Kemp AH, Felmingham KL, Liddell B, Olivieri G, Peduto A, et al. Enhanced amygdala and medial prefrontal activation during nonconscious processing of fear in posttraumatic stress disorder: an fMRI study. Hum Brain Mapp. 2008;29(5):517–23. https://doi.org/10.1002/hbm.20415.

152. Shvil E, Rusch HL, Sullivan GM, Neria Y. Neural, psychophysiological, and behavioral markers of fear processing in PTSD: a review of the literature. Curr Psychiatry Rep. 2013;15(5):358.

153. Bremner JD, Vermetten E, Schmahl C, Vaccarino V, Vythilingam M, Afzal N, et al. Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. Psychol Med. 2005;35(6):791–806.

154. Linnman C, Zeffiro TA, Pitman RK, Milad MR. An fMRI study of unconditioned responses in post-traumatic stress disorder. Biol Mood Anxiety Disord. 2011;1(1):8.

155. Rougemont-Bucking A, Linnman C, Zeffiro TA, Zeidan MA, Lebron-Milad K, Rodriguez-Romaguera J, et al. Altered processing of contextual information during fear extinction in PTSD: an fMRI study. CNS Neurosci Ther. 2011;17(4):227–36. https://doi.org/10.1111/j.1755-5949.2010.00152.x.

156. Gold AL, Shin LM, Orr S, Carson M, Rauch S, Macklin M, et al. Decreased regional cerebral blood flow in medial prefrontal cortex during trauma-unrelated stressful imagery in Vietnam veterans with post-traumatic stress disorder. Psychol Med. 2011;41(12):2563–72.

157. Lissek S, Bradford DE, Alvarez RP, Burton P, Espensen-Sturges T, Reynolds RC, et al. Neural substrates of classically conditioned fear-generalization in humans: a parametric fMRI study. Soc Cogn Affect Neurosci. 2013;9(8):1134–42.

158. Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152(7):973.

159. Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse – a preliminary report. Biol Psychiatry. 1997;41(1):23–32.

160. Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry. 2003;160(5):924–32.

161. Kitayama N, Vaccarino V, Kutner M, Weiss P, Bremner JD. Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. J Affect Disord. 2005;88(1):79–86.

162. Kühn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. Biol Psychiatry. 2013;73(1):70–4.

163. Woon FL, Sood S, Hedges DW. Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2010;34(7):1181–8.

164. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci. 2002;5(11):1242–7. https://doi.org/10.1038/nn958.

165. Babson KA, Feldner MT. Temporal relations between sleep problems and both traumatic event exposure and PTSD: a critical review of the empirical literature. J Anxiety Disord. 2010;24(1):1–15. https://doi.org/10.1016/j.janxdis.2009.08.002.

166. Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. J Clin Psychol. 2011;67(12):1240–58. https://doi.org/10.1002/jclp.20845.

167. Pace-Schott EF, Germain A, Milad MR. Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. Biol Mood Anxiety Disord. 2015;5:3. https://doi.org/10.1186/s13587-015-0018-9.

168. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev. 2008;12(3):185–95.

169. Mellman TA. Sleep and post-traumatic stress disorder: a roadmap for clinicians and researchers. Sleep Med Rev. 2008;12(3):165–7.

170. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev. 2008;12(3):169–84.

171. Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. Sleep. 2013;36(7):1059–68. https://doi.org/10.5665/sleep.2810.
172. Babson KA, Badour CL, Feldner MT, Bunaciu L. The relationship of sleep quality and PTSD to anxious reactivity from idiographic traumatic event script-driven imagery. J Trauma Stress. 2012;25(5):503–10. https://doi.org/10.1002/jts.21739.
173. Babson KA, Blonigen DM, Boden MT, Drescher KD, Bonn-Miller MO. Sleep quality among U.S. military veterans with PTSD: a factor analysis and structural model of symptoms. J Trauma Stress. 2012;25(6):665–74. https://doi.org/10.1002/jts.21757.
174. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry. 2013;170(4):372–82. https://doi.org/10.1176/appi.ajp.2012.12040432.

Chapter 3
Anxiety Disorders: A Feminist Ecological Approach

Rachel F. Rodgers, Rachel Berry, and Laura E. Fischer

Anxiety Disorders: A Feminist Ecological Approach

While traditional etiological models of mental disorders including anxiety disorders focus on the role of individual factors in the development and course of these concerns, other theoretical models such as the Feminist Ecological Model (for a visual representation, see 1, 2) place greater emphasis on the role of external sociocultural factors [1, 2]. The strengths of such a model lie in the consideration of individual- as well as systemic-level factors and a capacity to describe how systems may contribute to increasing risk for certain vulnerable groups. The goal of this chapter is to review the ways in which anxiety might be conceptualized using such a framework, including both theoretical and empirical work, as well as considering future directions.

The present chapter is grounded in a critical Feminist Ecological Model [3, 4] and considers how the different systems within which individuals are embedded may influence risk, presentation, and course of anxiety disorders. These systems may be conceptualized as concentric levels of influence that are embedded within a certain geographical and historical context. Each of these levels includes people or groups and organizations that may exert an influence on anxiety disorders. The most distal level of influence, referred to as the *macrosystem*, includes the economic and cultural context and sociocultural agents such as the media. The second, more proximal level is the *exosystem*, including the local community at a broader level, as well as public policy. The third, most internal, level of the model is the *microsystem* that

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includes elements in the person's environment offering immediate, face-to-face interactions and influences including, in particular, the interpersonal environment (family, friends, etc.). Finally, the *chronosystem*, reflecting changes in these structures across time, may constitute an additional layer of this model. In addition, a number of sociodemographic variables intersect with these systems, and moderate their effect, including gender and ethnicity, as well as other minority identities. Here, influences from the macrosystem, exosystem, as well as the impact of minority identities will be discussed. For example, ways in which the broader cultural, economic, and legal context may influence anxiety, as well as dimensions of identity such as gender and race/ethnicity, will be discussed. The microsystem will not be discussed in depth here, as the critical lens adopted places greater emphasis on the more distal levels as well as disparities related to minority identities.

Macrosystem

Over the past decades, a number of changes have occurred or accelerated at the societal level that may be related to risk for anxiety disorders. Specifically, discourses such as the focus on materialism, fast capitalism, as well as cultural and environmental threats that may in contrast increase risk for anxiety have been on the rise. These discourses have also been relayed by increasingly fast technologies that contribute to their social impact.

The Rise of Competitive Individualism

Social theorists identify individualization as one of the core processes of modernity [5]. This focus on individual achievement, combined with increasing freedom in terms of life choices related to occupation, identity, viewpoints, passions, etc., may lead to increasing anxiety to live up to social expectations [5]. Put more forcefully, and in reference to the rise of capitalism as an important aspect of modernity, some authors have described the social alienation and competitive individualism that are hallmarks of modern capitalist society as eroding self-esteem and identity [5]. Feeling deprived of value other than as an instrument of profit may contribute to this insecurity [6]. The rise of capitalism and its focus on paid employment has also been accompanied by the dissolution of traditional forms of community. However, the new order of economic individualism rather than providing a substitute structure for community may instead increase anxiety related both to the possibility of unemployment with its social and material consequences and to a system in which social value and status are precarious and require increasing efforts to establish [5].

In addition, the speeding up of society, in terms of information, relationships, political context, etc., increases the perception of the world being changing and

impermanent, heightening anxiety [7]. The fast-paced, hyper-stimulating, Western urbanized environment, with its increasing emphasis on the ever-changing self-identity, permeable social structure, and fragmented moral and epistemological structure, promotes uncertainty and highlights how little control individuals hold over events and their own circumstances [8]. Critical theorists have highlighted that while anxiety can be conceptualized as a subjective feeling of threatening uncertainty, circumstances are perceived as such when we are denied the cultural and social resources to make meaning of the situation to perceive a safe outcome [5].

Consistent with these theories, increased endorsement of core aspects of fast capitalism such as materialism has been shown to be associated with higher levels of anxiety [9, 10]. Similarly, investigations grounded in a framework of ontological security and risk society have supported the association between the pursuit of security and social status, for example, through home ownership and heightened feelings of anxiety [11]. Thus, modern economic individualism and the fast capitalism have been supported as contributing factors to heightened anxiety.

As just described, contemporary society increases risk for anxiety through its competitive individualism, as well as by dissolving the aspects of traditional society that served to contain and decrease anxiety. However, in addition to these elements related to its very nature, it has also been suggested that capitalism may deliberately leverage anxiety for profit through a number of pathways. Capitalism rests on a growth model that requires consumption, driven by the creation of "needs" or desires beyond basic necessity. Anxiety is a core mechanism in the creation of such needs and thus must be cultivated in consumers [7]. While this model underpins all of capitalist society, it is particularly illustrated in some industry sectors such as insurance and certain practices such as advertising [12].

In addition to this broad leveraging of anxiety as a driver of consumerism, the view of anxiety and anxiety disorders within the medical model may constitute another aspect of the macrosystem that it is important to consider. Without rejecting the usefulness and efficacy of medication (and manualized evidence-based psychotherapy approaches; see Chaps. 12 and 13 for details) in the treatment of cases of anxiety disorders, the exponential increase in the consumption of anxiety medication in Western settings since the 1950s has been examined through the lens of the growth of the pharmaceutical industry, the development of new types of anxiety medications, and the expansion of the number of diagnostic entities classified as anxiety disorders [13]. An in-depth description of these issues is beyond the scope of this chapter. However, certain authors have, for example, proposed that the recognition of social phobia and panic disorder as psychiatric disorders has been tightly intertwined with the development of their pharmaceutical treatments [14]. Including such considerations in the conceptualization of the sociocultural influences on anxiety disorders and their management may help to contextualize the multiple systems in which mental health disorders and their treatment are embedded and highlight the complex and multifactorial nature of these disorders.

Media

Many of the risks and uncertainties that exist at a national level are available to us only via their communication through the media [15]. Thus, the mass media are in some ways largely responsible for both our experience of events that occur at a geographic distance and also our perception and awareness of events that either *could* occur or occur on scales (time, size) that are outside of our capacity to perceive them. The awareness of these risks may be important, for example, for raising awareness around climate change or financial risk. However, at the same time, they serve to increase levels of anxiety in areas related to dimensions that would likely not have been in our awareness without the existence of mass media. In addition to the content of media that is heavily focused on hazard and risk, the increasing speed of the news cycle, the move toward news coverage on social media that is "real time," and the associated loss of contextual information that promotes meaning-making may also contribute to the capacity of media to increase anxiety. Furthermore, through the Internet and social media, coverage of disasters and violent events is provided by users in addition to media companies, with wide availability of graphic and potentially distressing imagery that may also increase levels of anxiety. For example, research has suggested that exposure to "real-time" media coverage of natural disasters such as the 2011 earthquake in Japan was associated with increased symptoms of post-traumatic distress in geographically distant individuals [16]. Consistent with this, empirical investigations of exposure to constant news broadcasting, and live news streams on social media, have supported the fact that the speeding up of information may contribute to escalating anxiety [16–18]. Finally, it has been highlighted how the media, as a for-profit industry embedded within a capitalist model, may benefit from arousing anxiety which is likely to lead to greater media consumption as a coping mechanism [19, 20]. In this way, the mass media represent important contributors to perceptions of risk and hazard that may contribute to risk for anxiety.

In sum, a number of macrosystem-level factors may contribute to raise risk for anxiety in contemporary Western society, as a result of the rise of modernity and fast capitalism, and media leveraging of anxiety as a means of increasing consumption within the economic growth model. Although scarce, empirical examinations of the relationships have lent preliminary support to the role of these factors in increasing anxiety.

Exosystem

At the exosystem level, social structures and institutions that have helped manage anxiety in certain groups, or provided resources for individuals experiencing anxiety in the past, may have declined in the recent decades. In addition, changes to the way in which healthcare, including assessment and treatment, is structured may influence current rates and presentations of anxiety.

The Decline of Religion and Community

In parallel with the rise in materialism, individualism, and fast capitalism, recent decades have witnessed a decline of religion, broadly characterized by a minimization of material possessions in preference of spiritual dimensions and a focus on collective well-being rather than individual gain. Spirituality and religiosity are multifaceted constructs involving both structural organized components and individual-level aspects, and it has been suggested that the decline of religion as a principal pillar of contemporary society may contribute to increasing risk for anxiety [21]. While a range of conceptualizations of the mechanisms through which religion improves mental health have been described, overall active engagement in religion has been described as an important coping mechanism [22] and an important resource for meaning-making, a framework regarding moral and ethical conduct, and reappraisal of events and problem-solving, all of which are identified as important skills for managing anxiety [23, 24]. In this way, religious tradition has been described as providing "ontological security," the removal of which increases anxiety [8]. Consistent with this, while findings are somewhat inconsistent, evidence has been found for a relationship between increased religiosity and lower levels of anxiety [23], as well as greater post-traumatic growth [24].

Economic and Sociopolitical Factors

A number of economic and sociopolitical factors may contribute to increased levels of anxiety including financial and political instability, as well as shifts associated with an increasingly globalized world. The rise of speculation, and the accompanying periods of financial crisis, has led over the past decades to increasing perceptions among the general population of the fragility of the financial market and related anxiety [25]. In addition, particularly in the US context, costs of education, healthcare, as well as debts incurred may increase worry and perception of risk and uncertainty and have been shown to be associated with increased anxiety [26].

In addition, over the last decades, a number of events have led to declining trust in governments [27, 28], as well as fast changes in the political landscape. Together these may serve to increase insecurity and anxiety [29]. Furthermore, it has been highlighted how such anxieties may also be leveraged for political gains [30], which could further contribute to higher levels of anxiety among the general population.

The Medical Model and Managed Care

In Western cultures, psychological phenomena such as anxiety are often viewed through the lens of the medical model. Two aspects of this model are particularly relevant here. First is the framing of anxiety as an index of psychopathology:

Inherent in the medical model is the underlying assumption that being free of anxiety is the cultural norm, and deviations from this can be considered aberrant. Second, within the medical model, psychopathology is largely considered to result from individual predispositions and characteristics. Conversely, from a Feminist Ecological Model perspective [4], anxiety can be conceptualized as an individual's response to the many intersecting systemic factors that impact how one navigates the world. The degree to which one experiences anxiety is a product of the interactions between individual-, micro-, exo-, and macrolevel processes. Thus, rather than conceptualizing anxiety as an individual vulnerability leading to excessive anxiety in the face of environmental demands, anxiety may be conceptualized as a response to the disproportionate stressors and demands placed on certain groups in conjunction with the lowest resources to meet them. However, the predominant view is oftentimes that of an individual vulnerability, acquired or innate. One example of this is the way some authors have described a gradual pathologization of shyness and the corresponding rise in rates of social anxiety disorder [31].

In addition to the ways in which the theoretical underpinnings of the medical model influence conceptualizations and definitions of anxiety, the managed care model that is the primary model of healthcare in the USA may also be an influence to consider. Specifically, managed care plays an important part in shaping the available treatment options for anxiety disorders and the preference for approaches that target the individual level, such as through medication or cognitive behavioral strategies, and focus on modifying an individual's symptoms such that they are able to function better within their environment rather than targeting the environment itself [32]. In sum, the decline of tradition and community coupled with growing economic circumstances and healthcare models that place both the responsibility and burden on the individual level as opposed to a system level may be related to anxiety disorders in multiple ways.

Microsystem and Individual Identities

At the core of the Feminist Ecological Model is the individual. Individuals are characterized by dynamic underlying biological, genetic, and psychological attributes that interact with the environment to produce complex experiences. In addition, individuals possess multiple identities such as age, sex, gender, race, ethnicity, sexual orientation, and physical ability. To a large extent, these identity factors are socially constructed and can shift over the course of an individual's lifespan. The ways in which individuals conceptualize their identities are related to interactions within their microsystem. A microsystem consists of an individual's daily face-to-face interactions with family members, friends, and members of their communities. For many, these interactions primarily take place in the home, in the neighborhood, within educational settings, in the workplace, or in houses of worship. Of course, individual characteristics and microsystem interactions are not static, nor do they

exist in isolation. Rather, these factors have dynamic interactions with processes occurring in exterior spheres of the Feminist Ecological Model, such as the exo-, macro-, and chronosystems. These broader local, regional, national, global, and sociohistorical factors interact with the individual and microsystem to impact individuals' mental health and psychosocial experiences.

Privilege and Power: The Minority Stress Model

The degree to which individuals experience anxiety is inextricably connected to their intersecting identity characteristics. Each individual holds a number of identities, and while these identities (e.g., gender or race) hold no inherently differential value and are largely socially constructed, individuals function as part of larger systems in which certain identities are privileged. The extent to which some identities are privileged while others are marginalized is largely a historical artifact. In the USA, those who have not identified as able-bodied, white, Christian, and male have historically been pushed to the margins of society and systematically disadvantaged [4]. At the same time, individuals with particular identities (i.e., female-identified) have been stereotyped as susceptible to anxiety due to a perceived underlying weakness. While there is truth in the assertion that individuals with particular identities may experience heightened anxiety, from a Feminist Ecological Model perspective, this is not the result of inherent weakness but rather a natural response to one's present and historical contexts.

The minority stress model posits that individuals of minority identity are subject to constant stress due to stigma and discrimination [33]. Stressors may be distal or proximal, though all are related to the social environment [34]. Such stressors may include internalized stigma, vigilance due to the expectation of rejection or discrimination by others, being subject to discrimination and violence by others, and structural or institutionalized discrimination or inequality. Thus, higher mental health risks in individuals with a visible (or potentially visible) minority status are not thought to be caused by the identity itself but by how the minority status is perceived in the culture at large. Whether the identity is possibly detectable by others (e.g., race, gender, age, some disabilities) or more easily concealed (e.g., sexual orientation, religious affiliation, invisible disabilities), the mental health of the individual is thought to be impacted by the actual or potential negative reaction by other people if the minority identity is made apparent.

Gender

One identity factor that may be related to anxiety is gender. Systemic factors that may contextualize an individual's experience of anxiety are explained below in relation to gender identities.

Cisgender Women   Although women are a majority of the US population, women hold less sociocultural power than men [35]. Women have higher rates of anxiety disorders than men, as well as some differences in presentation, course, severity, comorbidity, and treatment efficacy [36, 37]. Epidemiological studies of anxiety prevalence suggest rates of about one-third of women, compared to approximately 22% for men [36].

Sociocultural norms casting women as inferior to men may contribute to women's anxiety. Despite women frequently working outside the home, women still earn less than men and perform more hours of unpaid labor at home. Although women's professional aspirations are a factor, shifts in capitalist structures also necessitate that more women work for pay to cover their family's expenses. The poverty rate is higher among women, particularly in single-parent households headed by a woman [38]. Economic dynamics may take a toll on women's mental health. If society devalues women and their work, women may internalize this sense of inferiority. Alternatively, women may worry more due to real threats to financial stability resulting from lower wages and lack of career advancement opportunities resulting from workplace sexism. A lack of paid family leave and expensive childcare options also contribute.

Traditional gender roles, compounded by the recent superwoman ideal and pressure to combine multiple roles across different settings (home, work, etc.), may also contribute to greater levels of anxiety among women [39]. Women continue to disproportionately contribute to household work [40] and have been described as experiencing greater "mental load" referring to the burden frequently placed upon women to be the primary planner, supervisor, and executor of tasks related to professional, family, educational, and relational needs [41]. The effort required to juggle these various responsibilities, coupled with the social consequences of failing to meet gendered expectations, likely contributes to high rates of anxiety among women.

Misogyny presents macrolevel threats to women that may increase anxiety. This includes societal-level bias and discrimination against women as well as discriminatory or violent treatment by individuals in a woman's life. Women are more likely to be the victims of gender-based violence, often by individuals known to the victim. Violence may include rape or sexual assault, physical violence, or emotional abuse [42]. Although both men and women are victims and perpetrators of sexual and intimate partner violence, the rates of violence against women are much greater than those of men. Living in a society that constantly threatens violence against women, women may be more prone to experience anxiety symptoms such as restlessness, fatigue, impaired concentration, irritability, or a great deal of worry.

Transgender, Gender Nonbinary, and Gender Nonconforming Individuals   Transmen, transwomen, or nonbinary people experience stigma and discrimination-based stress with severe, negative mental health consequences. Trans people are disproportionately impacted by mental health struggles as compared to cisgender individuals. The rates of anxiety symptoms among trans people range from about 40% for transwomen to nearly 48% for transmen [43]. One important factor to consider in understanding anxiety among trans people is a lack of access to culturally

informed medical and mental health treatment. Trans people experience discrimination in clinical settings [44]. Additionally, they may be denied insurance coverage for healthcare services, including transition surgery. Many trans people thus avoid seeking needed medical care due to fears of mistreatment.

High rates of anxiety in trans and nonbinary individuals may be related to lack of social support and societal-level stigma and discrimination [43]. Trans people report significant rates of harassment, violence, and discriminatory treatment including physical attacks, being kicked out of the family home, verbal harassment, sexual assault, and workplace mistreatment [44]. As a direct result of discriminatory treatment, trans people are more likely to experience financial difficulties and to be poor [44]. About one-third of trans people live in poverty, with higher rates of homelessness and lower rates of homeownership. The unemployment rate among trans people is three times greater (15%) than the USA as a whole. Constant worry about when to conceal one's gender, fears that one will be outed, and fears of losing employment may be everyday stressors for trans people. Other stressors for the trans community include securing official government documents with their preferred name and gender, harassment by the police, or being denied access to a restroom of their choice or harassed/attacked when using the restroom. Therefore, a number of important contextual factors may be associated with anxiety levels in gender nonbinary individuals. When working with trans or gender nonbinary individuals who present with anxiety, it is imperative that clinicians ask about a wide range of systemic factors that may be contributing to the person's anxiety.

Cisgender Men   Although women are more frequently diagnosed with anxiety disorders, men are diagnosed with anxiety disorders at elevated rates [36]. Boys and men are impacted by misogyny and patriarchy and are socialized to strive for masculine ideals such as toughness and bravery. This socialization may make it difficult for men to accept and experience emotions such as fear and sadness. In addition, knowing that emotions such as fear are inconsistent with masculine ideals, men may experience increased shame and self-stigma. Furthermore, men who suffer from anxiety may be more likely than women to cope with difficult experiences using substances rather than engaging in coping mechanisms that may feel less consistent with stereotypical gender norms [45]. Given that substance abuse is a risk factor for attempted and completed suicide and that men complete suicide at higher rates than women, clinicians should be aware of the need to assess anxiety among cisgender male patients and consider the ways in which they may be coping with these difficult internal experiences [46].

Race/Ethnicity

Race or ethnicity may be another visible identity category that may play a role in the etiology, course, and treatment of anxiety disorders. Despite comparable or slightly lower lifetime prevalence rates of anxiety for ethnic/racial minority groups com-

pared to White European Americans, racial/ethnic minorities often experience greater symptom severity and functional impairment [47, 48]. Reasons for these disparities should be considered from a systems perspective. Among Black individuals, for example, this may be due in part to the fact that they are less likely to seek treatment for anxiety and receive specialized mental health treatment as compared to White individuals [49].

Ecological Considerations It is worth considering why lower rates of anxiety disorders among non-White individuals in the USA persist, despite the fact that individuals of racial or ethnic minority identity experience significantly greater social, economic, and political distress [48]. True prevalence rates may indeed be lower, or assessment tools and nosology systems may be insufficient to capture the experience of anxiety among non-White people. It is critical to consider how the etiology, presentation, and treatment of anxiety may differ for racial/ethnic minority people (see Chap. 4 for details on cross-cultural approaches to anxiety disorders).

Anxiety and the Legacy of Racism and Discrimination Stigma, discrimination, and systemic racism are all important factors to consider when assessing and treating anxiety among racial/ethnic minority people. Experiences of actual discrimination, perceived discrimination, and "racial battle fatigue," that is, mental and physiological experiences of constant subjection to racism and discrimination, may cause or exacerbate anxiety [50, 51]. An individual who worries constantly about many areas of life and feels constantly on edge may meet criteria for anxiety, but their anxiety must be contextualized within their everyday experiences. For example, people of ethnic/racial minority identity may enter everyday situation such as job interviews, opening a bank account, or interacting with police with heightened fear compared to racial majority people [51]. Thus, presentations that fall under the umbrella of anxiety systems may be a result of repeated exposure to systemic discrimination and may be best understood as a learned response to a threatening environment. Research findings suggest that the person's internal subjective experience of discrimination leads to negative mental health outcomes such as anxiety, whether or not the person was actually the target of overt racist behavior [52].

Systemic/institutional racist policies have also impacted generations of people of color and may relate to experiences of anxiety among racial/ethnic minority people [53]. Examples of such policies include academic policies (e.g., segregated schools), criminal justice issues (e.g., harsher sentencing guidelines for certain crimes), housing discrimination (e.g., policies related to homeownership), and civil rights issues (e.g., voting rights, voter suppression), among countless others. For example, Oliver and Shapiro [54] illuminate the historical, institutional practices that have led to the racial wealth gap between Black and White Americans. Such systemic factors should thus be considered when treating ethnic/racial minority individuals for anxiety disorders, as they may play a role in the etiology of anxiety in this population.

Anxiety, Immigration History, and Acculturation Immigration history and acculturation are vital to consider in experiences of anxiety among racial/ethnic minority

people. Age, reasons for, and circumstances of immigration are important factors. For example, a person who immigrated for higher education may have a different immigration experience when compared to a refugee immigrating involuntarily due to cultural, religious, political, or economic hardship [55, 56]. These experiences may be topics of clinical inquiry to understand how they may play a role in the person's experience of anxiety.

Level of acculturation (i.e., the degree to which individuals have adopted characteristics of a new host culture) is important to consider as well, so clinicians should be aware of how connected the client feels to their culture of origin and new culture [55]. Acculturation level may refer to language preference and comfort as well as identification with traditions and cultural norms of either culture. Some research has shown that identification with one's ethnic heritage is not protective against anxiety, although it may be protective against other forms of psychological distress [55]. Providers should thus inquire about the individual's life experiences related to immigration and acculturation, asking for the client's perspective on how these may be implicated as stressors that could cause or exacerbate anxiety symptoms.

Sexual Orientation

Sexual orientation identity is often defined as an enduring emotional, romantic, and/or sexual attraction to category or categories of gender, and can be considered in terms of behavior and identity, in addition to attraction [57]. For the purposes of this paper, the authors will use the term sexual orientation minority to refer primarily to those who identify as homosexual or gay, lesbian, bisexual, pansexual, or any other sexual orientation that falls outside of the dominant cisgender male-female attraction paradigm. The results of a nationally representative study from 2010 including just under 35,000 individuals suggest the rates of any anxiety disorder are about 41% for lesbian women and gay men, 58% for bisexual women, and 39% for bisexual men [58]. These rates are higher than for heterosexual individuals, with about 19% of heterosexual men and 31% of heterosexual women meeting criteria for an anxiety disorder over their lifetime.

Historically, sexual orientation minorities have been the target of discriminatory policies enacted by the US government. Though lesbian, gay, and bisexual (LGB) individuals have made strides in civil rights over the past several decades, these changes are fairly recent and subject to being upheld by the administration currently in office. The medical and mental health communities have also historically contributed to systemic discrimination of sexual orientation minority individuals through the inclusion of homosexuality as a sociopathic personality disturbance in the *Diagnostic and Statistical Manual of Mental Disorders* until 1973 [59]. Discrimination impacts individuals' decisions to conceal or disclose their sexual orientation to others, which is not a one-time occurrence but rather something one must negotiate in every relational context in one's life. While this may be a protec-

tive strategy to prevent harm befalling the person, concealment is also linked to stress, internalized homophobia, shame, and/or poor mental health outcomes [34]. Important historical and systemic factors impact the mental health of sexual orientation minorities, and mental health providers should take these factors into consideration when conceptualizing and particularly when treating anxiety in LGB people. For example, providers should inquire in which settings and relationships a person has revealed their sexual orientation, how others have reacted to the disclosure, and, if relevant, how the person feels about concealing their identity in some areas of their life.

Class

Socioeconomic status may interact with the incidence of anxiety and represents another important dimension to consider. As described above, macrolevel influences such as capitalism and individualism have led to increased income inequality, a shrinking of the middle class, and the consolidation of wealth among few Americans. Thus, in addition to those living below the poverty line, a growing number of Americans are facing financial insecurity and struggling to make ends meet [60]. Research has suggested the presence of a relationship between socioeconomic status and mental health outcomes [61–63] and specifically a range of anxiety disorders [64–67]. In addition, research suggests that perceived financial strain, regardless of income level, is associated with having an anxiety disorder [68].

Given that a disproportionate number of racial and ethnic minorities relative to white Americans live in poverty [69], these individuals may be impacted by both financial stressors in conjunction with other identity-based stressors mentioned above highlighting the importance of intersectional lenses when conceptualizing these individual-level factors. Importantly, the relationship between socioeconomic status and anxiety disorders is likely bidirectional, such that anxiety disorders both contribute to and result from lower socioeconomic status [48].

Age

Age constitutes another demographic variable that may be important to consider in the diagnosis and treatment of anxiety disorders, as individuals in different age groups and cohorts are subject to unique macro-, exo-, and chronosystem variables. The median age of onset for anxiety disorders is around age 11 [70], and rates of all anxiety disorders appear to increase with age from 18 to 64 years, with the highest rates reported among individuals in the 45–64 age bracket [71]. Children and adolescents may experience anxiety differently than adults due to macrolevel factors such as their family system, school environment, neighborhood, or social context. Young adults may experience anxiety due to the expectations related to this devel-

opmental stage, such as leaving the parental home, pursuing academic and/or professional goals, managing finances independently, and navigating relational issues such as friendships, romantic partnerships, and the possibility of parenthood. Anxious symptoms typically rise throughout adulthood, peaking in middle age [70]. Middle-aged adults experience many life-stage stressors including child-rearing, caring for aging parents, and financial and employment concerns. Anxiety disorders are the most common mental health issue affecting older adults, with generalized anxiety disorder being the most prevalent. Anxiety in older adults may be related to age-based discrimination, loneliness, chronic health conditions, functional difficulties, cognitive impairment, or adjustment issues related to life transitions such as retirement, not being able to live independently, or watching spouses and other same-age peers decline in health [72].

It is also important to consider systemic factors that change over time and thus affect birth cohorts differently, which are referred to as chronosystemic factors [73]. Twenge (2000) suggested that anxiety rates have increased over time from 1952 to 1993, arguing that an overall increase in anxiety occurred alongside major changes such as increases in violent crime, worries about nuclear war, fears of disease epidemics, and changing roles for women. She also notes that social connectedness and sense of community have decreased over time in Western cultures, evident in higher divorce rates, lower birth rates, later average age of marriage, and more individuals living alone. In addition to these chronosystemic factors, it is also worth considering how attitudes toward mental health and anxiety disorders have shifted over time toward increased public awareness and decreased stigma. These factors have likely contributed to individuals feeling more comfortable accurately reporting their symptoms and feeling less stigmatized in seeking treatment. When working with patients with anxiety disorders, clinicians should consider the systemic and lifespan factors contributing to the individual's experience of anxiety.

Conclusion

While predominant etiological frameworks place an emphasis on the individual when conceptualizing anxiety disorders, their risk factors, presentations, and course and treatment options, the current chapter aims to explore anxiety disorders through the lens of the Feminist Ecological Model. This model, in contrast, highlights how systems and institutions, as well as how these structures change over time, may contribute to rates of anxiety, through both its definition and framing and by increasing or decreasing social levels of risk factors for anxiety. In addition, we explore how a number of dimensions of identity place individuals at higher levels of vulnerability as related to these systemic factors. Importantly, these dimensions of identity may intersect with each other creating subgroups at particularly high risk for anxiety and poor outcomes. This lens may be useful for clinicians and researchers alike and contribute useful avenues for the prevention and treatment of anxiety disorders.

References

1. Ballou M, Matsumoto A, Wagner M. The Feminist ecological model. In: Ballou, Brown, editors. Rethinking mental health & disorder: feminist perspectives. New York: Guilford Press; 2002.

2. Rodgers RF, DuBois RH. Grief reactions: a sociocultural approach, Clinical Handbook of Bereavement and Grief Reactions. Humana Press, Cham: Springer; 2018. p. 1–18.

3. Bronfenbrenner U. Ecological models of human development. Read Dev Child. 1994;2(1):37–43.

4. Ballou MB, Brown LS. Rethinking mental health and disorder: feminist perspectives. New York: Guilford Press; 2002.

5. Wilkinson I. Anxiety in a 'Risk' Society. London: Routledge; 2002.

6. Horny K. The neurotic personality of our tine. New York: WV Norton; 1937.

7. Agger B. Fast capitalism: a critical theory of significance. Urbana: University of Illinois Press; 1989.

8. Giddens A. Modernity and self-identity: self and society in the late modern age. Stanford, CA: Stanford University Press; 1991.

9. Schroeder JE, Dugal SS. Psychological correlates of the materialism construct. J Soc Behav Pers. 1995;10(1):243–53.

10. Burroughs JE, Rindfleisch A. Materialism and well-being: a conflicting values perspective. J Consum Res. 2002;29(3):348–70.

11. Colic-Peisker V, Johnson G. Security and anxiety of homeownership: perceptions of middle-class Australians at different stages of their housing careers. Hous Theory Soc. 2010;27(4):351–71.

12. Wheatley JJ, Oshikawa S. The relationship between anxiety and positive and negative advertising appeals. J Mark Res. 1970;7:85–9.

13. Tone A. The age of anxiety: a history of America's turbulent affair with tranquilizers. New York: Basic Books; 2008.

14. Pérez-Álvarez M, García-Montes JM. The Charcot effect: the invention of mental illnesses. J Constr Psychol. 2007;20(4):309–36.

15. Beck U. Risk society: towards a new modernity. London: Sage; 1992.

16. Bui E, Rodgers RF, Herbert C, Franko DL, Simon NM, Birmes P, et al. The impact of internet coverage of the march 2011 Japan earthquake on sleep and posttraumatic stress symptoms: an international perspective. Am J Psychiatr. 2012;169(2):221–2.

17. Holman EA, Garfin DR, Silver RC. Media's role in broadcasting acute stress following the Boston Marathon bombings. Proc Natl Acad Sci. 2014;111(1):93–8.

18. Towers S, Afzal S, Bernal G, Bliss N, Brown S, Espinoza B, et al. Mass media and the contagion of fear: the case of Ebola in America. PLoS One. 2015;10(6):e0129179.

19. Altheide DL. Creating fear: news and the construction of crisis. New York: Routledge; 2017.

20. Burns R, Crawford C. School shootings, the media, and public fear: Ingredients for a moral panic. Crime Law Soc Chang. 1999;32(2):147–68.

21. Altemeyer B. PERSPECTIVES: the decline of organized religion in Western civilization. Int J Psychol Relig. 2004;14(2):77–89.

22. Hathaway WL. Clinically significant religious impairment. Ment Health Relig Cult. 2003;6(2):113–29.

23. Shreve-Neiger AK, Edelstein BA. Religion and anxiety: a critical review of the literature. Clin Psychol Rev. 2004;24(4):379–97.

24. Park CL. Religion and meaning. Handb Psychol Relig Spiritual. 2005;2:357–79.

25. Engelberg J, Parsons CA. Worrying about the stock market: evidence from hospital admissions. J Financ. 2016;71(3):1227–50.

26. Fitch C, Hamilton S, Bassett P, Davey R. The relationship between personal debt and mental health: a systematic review. Ment Health Rev J. 2011;16(4):153–66.

27. Chanley VA, Rudolph TJ, Rahn WM. The origins and consequences of public trust in government: a time series analysis. Public Opin Q. 2000;64(3):239–56.
28. Foster C, Frieden J. Crisis of trust: socio-economic determinants of Europeans' confidence in government. European Union Politics. 2017;18(4):511–35.
29. Browning CS. Brexit, existential anxiety and ontological (in) security. Eur Secur. 2018;27(3):336–55.
30. Albertson B, Gadarian SK. Anxious politics: democratic citizenship in a threatening world. New York: Cambridge University Press; 2015.
31. Scott S. The medicalisation of shyness: from social misfits to social fitness. Sociol Health Illn. 2006;28(2):133–53.
32. Clark DM. Implementing NICE guidelines for the psychological treatment of depression and anxiety disorders: the IAPT experience. Int Rev Psychiatry. 2011;23(4):318–27.
33. Meyer IH. Minority stress and mental health in gay men. J Health Soc Behav. 1995;36:38–56.
34. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull. 2003;129(5):674–97.
35. Howden LM, Meyer JA. Age and sex composition: 2010. In: Bureau USC, editor. Washington, DC: U.S. Department of Commerce Economics and Statistics Administration; 2011. p. 1–15.
36. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res. 2011;45(8):1027–35.
37. Vesga-López O, Schneier F, Wang S, Heimberg R, Liu S-M, Hasin DS, et al. Gender differences in generalized anxiety disorder: results from the National Epidemiologic Survey on alcohol and related conditions (NESARC). J Clin Psychiatry. 2008;69(10):1606.
38. Edin K, Kissane RJ. Poverty and the American family: a decade in review. J Marriage Fam. 2010;72(3):460–79.
39. Thornton B, Leo R. Gender typing, importance of multiple roles, and mental health consequences for women. Sex Roles. 1992;27(5–6):307–17.
40. Craig L, Baxter J. Domestic outsourcing, housework shares and subjective time pressure: gender differences in the correlates of hiring help. Soc Indic Res. 2016;125(1):271–88.
41. Horizons B. Bright Horizons modern family index. 2017.
42. Catalano SM. Intimate Partner Violence – attributes of Victimization, 1993–2011: US Department of Justice, Office of Justice Programs, Bureau of Justice Statistics; 2013. p. 1–19.
43. Budge SL, Adelson JL, Howard KA. Anxiety and depression in transgender individuals: the roles of transition status, loss, social support, and coping. J Consult Clin Psychol. 2013;81(3):545.
44. James SE, Herman JL, Rankin S, Keisling M, Mottet L, Anafi M. Executive summary of the report of the 2015 U.S. transgender Survey. Washington, DC: National Center for Transgender Equality; 2016.
45. Cox BJ, Swinson RP, Shulman ID, Kuch K, Reichman JT. Gender effects and alcohol use in panic disorder with agoraphobia. Behav Res Ther. 1993;31(4):413–6.
46. Mościcki E. Gender differences in completed and attempted suicides. Anals of Epidemiology. 1994;4(2):152–8.
47. Breslau J, Aguilar-Gaxiola S, Kendler KS, Su M, Williams D, Kessler RC. Specifying race-ethnic differences in risk for psychiatric disorder in a USA national sample. Psychol Med. 2006;36(1):57–68.
48. Himle JA, Baser RE, Taylor RJ, Campbell RD, Jackson JS. Anxiety disorders among African Americans, blacks of Caribbean descent, and non-Hispanic whites in the United States. J Anxiety Disord. 2009;23(5):578–90.
49. Brenes GA, Knudson M, McCall WV, Williamson JD, Miller ME, Stanley MA. Age and racial differences in the presentation and treatment of generalized anxiety disorder in primary care. J Anxiety Disord. 2008;22(7):1128–36.
50. Smith W, Allen W, Danley L. "Assume the position...you fit the description": Psychosocial experiences and racial battle fatigue among African American male college students. Am Behav Sci. 2007;51:551–78.

51. Soto JA, Dawson-Andoh NA, BeLue R. The relationship between perceived discrimination and generalized anxiety disorder among African Americans, afro Caribbeans, and non-Hispanic whites. J Anxiety Disord. 2011;25:258–65.

52. Williams DR, Mohammed SA. Discrimination and racial disparities in health: evidence and needed research. J Behav Med. 2009;32(1):20–47.

53. Clair M, Denis JS. Sociology of racism. In: Wright JD, editor. The international encyclopedia of the social and behavioral sciences, vol. 19. 2nd ed. Amsterdam: Elsevier; 2015. p. 857–63.

54. Oliver M, Shapiro T. Black wealth/white wealth: a new perspective on racial inequality. Hoboken: Routledge; 2006.

55. Kartal D, Alkemade N, Eisenbruch M, Kissane D. Traumatic exposure, acculturative stress and cultural orientation: the influence on PTSD, depressive and anxiety symptoms among refugees. Soc Psychiatry Psychiatr Epidemiol. 2018;53(9):931–41.

56. Hong JJ. Anxiety disorders in Asians and Asian Americans. Asian J Psychiatr. 2014;7:74–6.

57. Lourie MA, Needham BL. Sexual orientation discordance and young adult mental health. J Youth Adolesc. 2017;46(5):943–54.

58. Bostwick WB, Boyd CJ, Hughes TL, McCabe SE. Dimensions of sexual orientation and the prevalence of mood and anxiety disorders in the United States. Am J Public Health. 2010;100(3):468–75.

59. Drescher J. Out of DSM: Depathologizing homosexuality. Behav Sci. 2015;5(4):565–75.

60. Survey W-BaBN. Financial distress among American families. Urban Institute; 2019. p. 1–12. https://www.urban.org/sites/default/files/publication/99771/financial_distress_among_american_families_0.pdf.

61. Baum A, Garofalo J, Yali A. Socioeconomic status and chronic stress – does stress account for SES effects on health? Socioecon Status Health Ind Nations. 1999;896:131–44.

62. Lantz PM, House JS, Mero RP, Williams DR. Stress, life events, and socioeconomic disparities in health: results from the Americans' changing lives study. J Health Soc Behav. 2005;46(3):274–88.

63. Turner R, Wheaton B, Lloyd D. The epidemiology of social stress. Am Sociol Rev. 1995;60(1):104–25.

64. Grant BF, Goldstein RB, Chou SP, Huantg B, Stinson FS, Dawson DA, et al. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the wave 2 National Epidemiologic Survey on alcohol and related conditions. Mol Psychiatry. 2009;14(11):1051–66.

65. Mondin TC, Konradt CE, de Azevedo CT, de Avila QL, Jansen K, de Mattos LD, et al. Anxiety disorders in young people: a population-based study. Brazilian J Psychiatry. 2013;35(4):347–52.

66. Regier D, Narrow W, Rae D. The epidemiology of anxiety disorders – the epidemiologic catchment-area (ECA) experience. J Psychiatr Res. 1990;24:3–14.

67. Wittchen H, Stein M, Kessler R. Social fears and social phobia in a community sample of adolescents and young adults: prevalence, risk factors and co-morbidity. Psychol Med. 1999;29(2):309–23.

68. Dijkstra-Kersten SM, Biesheuvel-Leliefeld KE, van der Wouden JC, Penninx BW, van Marwijk HW. Associations of financial strain and income with depressive and anxiety disorders. J Epidemiol Community Health. 2015;69(7):660–5.

69. Semega J, Fontenot K, Kollar M. Income and Poverty in the United States. In: Bureau USC, editor. . Washington, DC: U.S. Government Printing Office; 2017. p. i–59.

70. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015;17(3):327.

71. Somers JM, Goldner EM, Waraich P, Hsu L. Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. Can J Psychiatr. 2006;51(2):100–13.

72. Lenze EJ, Wetherell JL. A lifespan view of anxiety disorders. Dialogues Clin Neurosci. 2011;13(4):381–99.

73. Twenge JM. The age of anxiety? The birth cohort change in anxiety and neuroticism, 1952–1993. J Pers Soc Psychol. 2000;79(6):1007.

Chapter 4
Two Peas in a Pod? Understanding Cross-Cultural Similarities and Differences in Anxiety Disorders

Anushka Patel and Devon Hinton

Chapter Overview

Although anxiety disorders are universal, they evince patterns of cross-cultural variability in their prevalence, explanations, and clinical presentations. In this chapter, we explore the global and domestic prevalence of anxiety disorders. We present how explanations of anxiety (i.e., explanatory models) and display rules (i.e., culturally sanctioned modes of expression) may partially account for differences in prevalence rates. We also discuss locally meaningful idioms of distress and syndromes to assess, followed by key transcultural and transdiagnostic targets that may complement traditional approaches to assessment and conceptualization of anxiety. Next, we synthesize observed differences in the clinical presentation of three major anxiety disorders. The goal of this synthesis is to provide case examples of how panic disorder (PD), social anxiety disorder (SAD), and generalized anxiety disorder (GAD), all manifest in subtly distinct ways across cultural groups. Throughout this chapter, we invoke examples from diverse cultural groups – in the United States and in global settings – to represent a breadth of cultural groups.

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Cross-Cultural and Cross-Ethnic Differences in Prevalence of Anxiety Disorders

A systematic review of 87 studies across 44 countries suggests that the current prevalence of anxiety disorders varies across cultures as it ranges from 2.4% to 29.8% (1). After adjusting for methodological variation between studies, the current global prevalence of all anxiety disorders is estimated at 7.3% (4.8–10.9%). This estimate reflects a range from 5.3% (3.5–8.1%) among African cultures to 10.4% (7.0–15.5%) in Anglo-European cultures. Anxiety disorders have a multifactorial etiology, consisting of interactive genetic and environmental influences (2). In line with this, a systematic review of anxiety disorders (1) also found that multiple factors such as gender, age, urbanicity, conflict exposure, and socioeconomic status explained significant portions of variance in the global prevalence of anxiety disorders. Examination of one factor – cultural group – indicated that the risk of having an anxiety disorder was 20–50% lower in non-Anglo-European cultural groups (1). Within the United States, a similar trend was noted. That is, the observed race–ethnic differences in anxiety disorders deduced from the Collaborative Psychiatric Epidemiology Studies suggest that Caucasian Americans met criteria for PD, SAD, and GAD at higher rates than Latin Americans, African Americans, or Asian Americans (3).

However, the pattern of prevalence within cultural minority groups highlights a more nuanced picture. Studies have shown that more Latin-Americans born in the United States tend to meet criteria for psychiatric disorders compared to Latino/a/x individuals who immigrated to the United States in a phenomenon termed the "immigrant paradox" (4, 5). The differing prevalence of anxiety disorders within cultural groups that share an ethnic origin suggests the need to assess and address contextual factors such as acculturation (6) that may confer risk of developing or maintaining anxiety disorders for minority cultural groups.

Despite anxiety disorders being relatively common phenomena, there are major disparities in access to and utilization of care among minority cultural groups (7). The literature on service utilization suggests that cultural minority groups, such as Latin Americans and African Americans, tend to underutilize services for anxiety disorders compared to their Caucasian counterparts (8, 9). One hypothesized reason for the underutilization of services relates to miscommunications in the clinical encounter. Specifically, linguistic barriers, cultural biases, differences in explanatory models, mismatch between expectations of clinician–client communication, and discrepancy in emphasized values between clinicians and clients have been identified as key problems in a systematic review of the literature on medical miscommunication (10). Such barriers necessitate that clinicians understand clinically distinct presentations.

The goal of the following sections of this chapter are threefold: (1) to review how clinical presentations of anxiety may differ across cultures due to differences in explanatory models and display rules surrounding appropriate expression of distress; (2) to discuss use of transcultural and transdiagnostic constructs to assess

anxiety to facilitate improved recognition across cultures; and (3) to provide case examples of culturally informed work that embodies these approaches to understanding cross-cultural differences in common anxiety disorders.

Cross-Cultural Differences in Explanatory Models and Display Rules

The variable prevalence of anxiety disorders has been partially attributed to variable recognition across cultural contexts due to differences in how people experience, express, and explain their anxiety. Anxiety, like other forms of psychological distress, constitutes a patterned cultural communication that is meaningful within the social and interpersonal contexts an individual is embedded in (11). One way to discern what is considered pathological anxiety in a cultural context is by understanding the cultural concepts of distress (CCDs) and explanatory models of anxiety.

Cultural concepts of distress include idioms of distress and syndromes. Idioms refer to ways of communicating through complaints that are culturally understood as conveying distress (11). Syndromes are similar to DSM entities, wherein symptoms form constellations of a prototype that members and healthcare providers of a population recognize as a disorder (12). An example of an idiom is *nervios* or nerves in Latin American communities. This is a general term used to convey vulnerability to stressful events and includes a wide range of somatic, emotional, and functional impairments such as aches in the brain, irritability, nervousness, and tearfulness (13, 14). An example of a syndrome in this same cultural group is *ataque de nervios*, or attack of the nerves, which features uncontrollable emotional dysregulation indexed by shouting, crying, and dissociation (12). Notably, CCDs do not always map onto universal psychiatric categories developed through research with Anglo-European populations (15). There are many benefits to assessing CCDs, including recognizing culturally salient distress in a multidimensional manner, improving treatment access, and reducing cultural barriers to care by framing the illness and treatment in culturally consonant non-stigmatizing terms (15–17).

Explanatory models refer to a cultural group's understanding and explanation of a disorder. The explanatory model encompasses putative causes of a disorder, its recognizable symptoms, ideas related to its remission, the best coping mechanisms, and indicated help-seeking (18). Also, cultural groups differ widely in what is socially acceptable to emotionally express. These implicit emotional display rules (19) dictate how social interactions are transacted. Specifically, what evokes an emotion, how it is expressed, and what the consequences for its expression are can all vary by cultural setting. What is socially recognized within the constraints of display rules then determines what kinds of emotional expressions can enable an individual to acquire help in a given context. As cultural values shape the expression of emotions and communication styles (20), these values also interact with the available help in the healthcare system to further influence the ways in which people seek and acquire help (17, 21).

For example, psychologically explaining one's distress by discussing the impact on self-esteem is recognized as a clear sign of distress in Anglo-European groups partly because the healthcare system these groups have access to have psychologists who readily recognize psychological distress and attend to it (17). In contrast, cultural groups without access to psychologists may be more prone to present with somatic problems to a primary care provider. While the presenting complaints may differ between individuals in each cultural group, these differences could be attributed to what is socially acceptable and culturally recognized as a form of valid suffering that can then be readily helped. Indeed, somatic complaints are common across many cultural groups, including Anglo-Europeans, but their meanings and salience may differ across cultures (22). Similarly, while clinical features of a disorder may be cross-culturally invariant, the meanings attached to the experience of the symptoms may differ widely (23). According to a review synthesizing research across Asian Americans, individuals with externalizing symptoms (e.g., angry outbursts) recognize these problems as requiring help because they disrupt social harmony in apparent ways, whereas internalizing symptoms are discounted and underreported, as they are less likely to view these as true problems that warrant professional help (23).

Challenges with recognizing distress in medical encounters can lead to misdiagnosis, stigma, and underutilization of services. Therefore, querying for symptoms in a contextually specific manner can enable more thorough assessment of all relevant anxiety symptoms an individual from a non-dominant cultural group has contended with. Learning subjective worldviews of what is considered pathological or normative is crucial for discerning whether certain symptoms are considered impairing in a cultural context. Eliciting explanatory models can prevent underdiagnosis or miscategorization of otherwise normal distress (11, 17, 24).

Explanatory models are influenced by the surrounding culture but are also individualized (21). For example, in describing distress, one client may emphasize psychological causes of their worry by highlighting what he, she, or they are "thinking a lot" about (see below for further discussion of this idiom). Another client might instead highlight that "thinking a lot" triggers uncomfortable physical sensations, such as heart palpitations, and these physical sensations go on to trigger anxiety. These two hypothetical clients may well invoke "thinking a lot" as a common explanation of anxiety; however, there are subtle distinctions in the relationship that "thinking a lot" has in triggering other cascading symptoms. These explanations are also meaningfully linked with the kinds of cures that each client may seek and respond to. While treating worry and rumination directly may be the best strategy for the first client, it is possible that targeting physiological arousal may be more sensible for the second client. Such variations in explanatory models of anxiety warrant careful individualized assessment to improve diagnosis and inform culturally responsive treatment plans.

The two commonly used assessment tools to elicit explanatory models are the explanatory model interview catalogue (EMIC) (18) and the cultural formulation interview (CFI) in the DSM 5 (12). Both these interviews can be modified for any disorder and cultural group. Other promising assessment tools are the "Thinking a

Lot" questionnaire and "Somatic Symptom and Syndrome Inventory" developed by Hinton and colleagues (25, 26) that are also suited for adaptation across cultural groups for a range of anxiety disorders. Use of such assessment tools can improve culturally sensitive case conceptualization of anxiety, and enhance recognition of the treatment targets.

Transdiagnostic Constructs Shaping Anxiety Disorders Across Cultures

While knowledge of explanatory models can improve recognition of idiographic symptom presentations, assessing for cognitive, affective, and somatic processes that universally undergird anxiety disorders is equally necessary for making accurate diagnoses. Knowledge of these mechanisms can improve conceptualization of anxiety, from understanding its etiology to explaining its maintenance over time. Transdiagnostic processes that are common across multiple mood disorders and cultural settings include repetitive negative thinking (27), often expressed as "thinking a lot" (28, 29); anxiety sensitivity (30–32); and somatic complaints (15, 21, 22).

"Thinking a Lot"

Repetitive negative thinking is described in many cultures as "thinking a lot." Notably, this idiom has been used to convey both rumination about past events and future-oriented worries. "Thinking a lot" is a cognitive vulnerability factor that undergirds many psychiatric problems, including depressive and anxiety disorders. As such, "thinking a lot" is an idiom that indicates current distress and the probable presence of "thinking a lot"-induced symptoms and catastrophic cognitions (28). While "thinking a lot" has been documented widely in cross-cultural studies (29) and is considered a transcultural phenomenon, the specific aspects of this phenomenon likely differ by cultural group. In particular, there are differences in the *types* of catastrophic cognitions associated with anxiety across cultures (11). That is, the meaning of anxiety symptoms varies across cultures, which partially accounts for the differences in how anxiety symptoms are considered in a given context. For instance, the content of cognitions (e.g., depressive rumination, worries, trauma recall) and types of catastrophic cognitions elicited during an episode of "thinking a lot" may vary by cultural group. Similarly, cognitive, affective, and somatic symptoms triggered by "thinking a lot" (e.g., poor concentration, dysphoric mood, and dizziness) may also vary by cultural group. Finally, the degree to which "thinking a lot" is considered abnormal and impairing and the coping strategies and help-seeking behaviors associated are also likely to vary by cultural group. Altogether, the transcultural model of "thinking a lot" can be best used by adapting it to elicit specific causal models that "thinking a lot" may play in generating anxiety disorders.

Anxiety Sensitivity

Anxiety sensitivity (AS), a dispositional vulnerability factor, is defined as the propensity to fear physical, cognitive, and social consequences that arise from experiencing anxiety (33). Examples of the same include fear of experiencing a heart attack from increased heart palpitations during anxiety, fear of going "crazy," and fear of how others evaluate the individual during an anxious state. Anxiety sensitivity tends to compound anxiety symptoms because it makes an individual have a "fear of fear" by believing that anxiety symptoms are harmful, thereby escalating the original fear in recurring feedback loops. Evidence suggests that anxiety sensitivity is another transdiagnostic and transcultural construct observed among many cultural groups, including Russians (34), Canadians, Mexicans, French, Dutch, Spanish, White Americans (35), Latin-Americans (36), and Cambodian refugees (31, 37). However, the relationship between anxiety sensitivity and amplification of anxiety across all cultures is nuanced. For instance, a study comparing amplification of somatic complaints among Latino and non-Latino youth found that fearing anxiety symptoms is normative in Latin American culture (38). As a result, anxiety sensitivity did not predict somatic problems for Latino youth in the same manner that it did for non-Latino youth. Notably, anxiety sensitivity might result from catastrophic cognitions about anxiety symptoms that vary across cultures. For example, the degree of fear of an anxiety-related somatic symptom may vary by whether a culture considers it dangerous and is indicative of imminent physical disaster. This is an example of how anxiety sensitivity may vary across cultures in overall severity and the types of anxiety symptoms that most provoke fear. These differences in anxiety sensitivity, and attributed consequences of anxiety, have major implications for the cross-cultural diagnosis and treatment of anxiety.

Somatization

Somatization, the tendency to experience and express physical complaints as a manifestation of psychosocial distress (39), constitutes a salient part of the clinical presentation of anxiety in many cultural groups (15, 21, 22, 38, 40). Although somatization is a common expression of distress transculturally, the literature indicates that there is a cultural patterning of which somatic symptoms are more or less emphasized (41, 42). This may be because of communicative style or the prominence of catastrophic cognitions about somatic complaints. Sometimes somatic problems are experience-near categories that are highly related to self-perceived well-being. For instance, one study eliciting emotional lexica between two different Ghanaian ethnic groups found that emotions were often described in terms of the somatic sensations they produced (43). For cultural groups whose primary complaints are somatic, assessing and addressing affective, cognitive, and behavioral correlates of these complaints can improve treatment outcomes. Specifically, assess-

ment of somatic complaints can improve the identification of key treatment targets – such as associated catastrophic cognitions about the somatic sensations – and increase treatment adherence. For example, a treatment study of adapted cognitive behavioral therapy designed to treat posttraumatic stress disorder among Latin American women reduced the severity of somatic symptoms accompanying *ataque de nervios* and led to other favorable treatment outcomes overall (44). Similarly, cognitive behavior therapy adapted for Cambodian refugees also resulted in reductions in key somatic complaints, such as orthostatic dizziness, that are central to this cultural group's goals for treatment (30, 45).

Case Examples: Conceptualizing Anxiety Across Cultures

The following sections discuss cultural considerations in approaching common anxiety disorders with diverse cultural groups. These cultural considerations link the relationship of local CCDs, expressed via idioms of distress and syndromes, to transcultural and transdiagnostic constructs related to anxiety through case studies.

Cultural Considerations for Panic Disorder (PD): Khyâl Attacks *and* Ataque De Nervios

Panic disorder, as defined in the DSM 5, is an anxiety disorder characterized by recurrent "out-of-the-blue" panic attacks consisting of physiological and cognitive reactions that crescendo within a 10-minute timeframe. Panic attacks cause the individual distress over experiencing the next panic attack or trigger a significant shift in behaviors designed to avoid future panic attacks (12).

Panic disorder varies considerably across cultures in symptoms and explanatory models, as has been demonstrated in detail for two cultural groups: Cambodian refugees and Latin American immigrants. *Khyâl attacks* are a cultural variant of panic attacks observed among Cambodian refugees. The phenomenology of panic-like symptoms in *khyâl attacks* includes neck soreness, tinnitus, and dizziness that are triggered by various cues that include anxiety itself, worry, or "thinking a lot," certain smells, and standing up (46, 47). Some *khyâl attacks* also occur out of the blue, and all episodes include a strong fear of bodily disaster.

Similarly, several Latin American groups report a cultural variation of PD termed *ataque de nervios*. Lewis Fernandez and colleagues (2002) studied a group of Dominican and Puerto Rican participants reporting both *ataque de nervios* and PD to understand overlaps and distinctions between these syndromes (48). Commonalities between *ataque de nervios* and PD include the following: recurring episodes, fearfulness during the episode, and maladaptive behavioral changes (e.g., avoidance of triggers) following the episode. However, *ataque de nervios* and PD

also differ significantly. For example, *ataque de nervios* is typically triggered by interpersonal stress and fights in the family unit compared to classic panic attacks in PD that ostensibly occur out of the blue. Similarly, *ataque de nervios* differs from classic panic attacks seen in PD in that they are followed by feelings of relief rather than further fear. Finally, *ataque de nervios* episodes do not crescendo within 10 minutes, but can sometimes last for hours on end. *Ataque de nervios* is also accompanied by distinct phenomenology – such as feeling out of control, hysterical crying, and anger that are not characteristic of PD. Notably, the symptom of trembling becomes a focal point for Latino/a/x individuals, and it is attributed to *ataque de nervios* rather than a panic attack. Attention given to trembling amplifies other related physiological symptoms, which are further catastrophized to trigger an *ataque de nervios* episode.

The transcultural and transdiagnostic constructs discussed in this chapter have been theorized as central mechanisms in the generation of panic sensations for Cambodian refugees and Latin American immigrants respectively. The cognitive theory of PD can be applied to explaining panic symptoms among Cambodian refugees to explain how "thinking a lot" about specific somatic symptoms leads to PD (46). According to the cognitive theory of panic, catastrophic cognitions about the dangerousness of panic symptoms can elevate the symptoms to produce a true panic attack (47). However, the *types* of catastrophic cognitions that can trigger panic are culturally shaped based on which somatic experiences are considered dangerous and aversive in a cultural context. As panic attacks are accompanied by numerous sensations, certain sensations may be more or less salient for specific cultural groups. For instance, Cambodian refugees fear the somatic sensation of dizziness as a part of panic attacks (46). Cambodian refugees' explanatory model of panic-like symptoms holds that dizziness is caused by a wind-like substance termed *khyâl* surging upward through the body where it pushes on the lungs (possibly causing asphyxia), hits the heart (possibly causing cardiac arrest), distends the neck vessels (possibly causing ruptured vessels), and swirls in the cranium (possibly causing syncope). An episode of "thinking a lot" can fuel these fears by amplifying attention on uncomfortable sensations and creating expectancies of aversive physiological states to eventually produce panic attacks (28). As a result, when "thinking a lot," Cambodians may avoid specific behaviors, such as standing up quickly, or turning their head quickly, for fear of triggering a *khyâl attack*.

The affective vulnerability factor of anxiety sensitivity can be applied to explain the nature of panic-like symptoms accompanying *ataque de nervios* among Latin American immigrants. According to work conducted by Hinton and colleagues, fear of negative affect and fear of arousal symptoms strongly predicted severity of self-reported symptoms among Latin Americans of Caribbean origin (49). The authors present a model to explain the role that anxiety sensitivity plays in the generation of *ataque de nervios*. In this model, an individual may become upset, anxious, or angry over a negative event (e.g., death in the family, impending loss, or an argument). The initial conditions of distress may produce other uncomfortable psychological and somatic sensations. For instance, feeling nervous may activate autonomic arousal to produce hyperventilation (50). In turn, these signs can create a

rapid escalation of other uncomfortable sensations that can increase the chances of experiencing an *ataque de nervios* episode as the individual might interpret these sensations as the onset of an episode. Hence, the purported mechanisms that explain initial sensations and a subsequent *ataque de nervios* episode are multiplex. An individual may be triggered by catastrophic cognitions about the sensations, attributing them to imminently dangerous conditions (e.g., a heart attack), and the resulting internal sensations and fear may escalate into a vicious cycle as fear produces symptoms and symptoms produce more fear.

Scholarship on Cambodian refugees and Latin American immigrants suggests that the interpretation of symptoms, which is influenced by local ideas of human physiology and mind–body connections (i.e., ethnophysiology), forms a prominent part of the explanatory model of panic-like symptoms. In turn, these ideas influence particular help-seeking behaviors that may or may not be compatible with Westernized psychological approaches to treating PD. Therefore, eliciting the explanatory model can improve a clinician's ability to strategically target specific cognitions for modification as part of culturally responsive treatment (51).

Cultural Considerations for Social Anxiety Disorder (SAD): Taijin kyofusho

Social anxiety disorder, as defined in the DSM 5 (12), is characterized by a fear of being judged, negatively evaluated, or rejected in social situations or during a performance. As with other anxiety disorders, such symptoms must be distressing, impairing, and not attributable to other conditions to fulfill criteria for SAD. As social anxiety stems from fear of social evaluation, it is necessarily shaped by broader cultural influences that dictate appropriate social behaviors and the consequences for violating the same. Indeed, the cultural norms guiding social interactions have been found to influence the presentation, and recognition, of social anxiety because cultures differ in how much they emphasize social cohesion and the costs of violating social norms (52). There is some support for the hypothesis that the mismatch between an individual's cultural orientation and the broader societal values is associated with greater severity of SAD (53).

While Asian Americans are consistently diagnosed with SAD more often than their Caucasian counterparts (54) and collectivistic cultures tend to have a greater fear of blushing, collectivistic cultures also tend to accept socially reticent behaviors more than individualistic cultures (55). These seemingly contradictory findings indicate that social reticence and associated features, such as fear of negative evaluation, may be more tolerated and considered less pathological in collectivistic cultures that value obedience to social norms.

A framework to conceptualize culturally specific presentations of SAD is summarized by Hofmann and Hinton (2014), who support an interactionist perspective of individual and environmental factors shaping culturally distinct SAD presentations (56). Specifically, the cultural views on ethnophysiology (i.e., local ideas of

mind–body relations) interact with contextual factors (i.e., social rules). The distinct presentation of SAD is well illustrated among the Japanese and Koreans, who report a local syndrome, *taijin kyofusho.* This syndrome overlaps with SAD in that it is also characterized by fear of social situations. While the social-evaluative concerns of *taijin kyofusho* fulfill criteria for SAD, the fears are also qualitatively distinct from SAD. The focal point of the concern in social situations for a Japanese or Korean individual with *taijin kyofusho* is about making *others* uncomfortable. The DSM 5 provides the example of a client with *taijin kyofusho* possibly reporting a complaint such as "My gaze upsets people so they look away and avoid me" (12). The Japanese diagnostic system further subclassifies this syndrome into four types reviewed by Hofmann and colleagues (57): *sekimen-kyofu* (characterized by a fear of blushing), *shubo-kyofu* (characterized by a fear of a deformed body), *jikoshisen-kyofu* (characterized by a fear of eye-to-eye contact), and *jikoshu-kyofu* (characterized by a fear of one's own foul body odor). While the first two overlap with SAD, the last two share features with body dysmorphic disorder as conceptualized in the DSM 5 (57). These examples demonstrate how fears related to social evaluation actually stem from offending others. Applying the interactionist framework to understanding *taijin kyofusho,* Hofmann and Hinton (2014) observe "['*Taijin kyofusho*'] is an example of a culture-specific form of an anxiety disorder in which contextual factors predominate" (54p4).

There is a limited literature that comprehensively integrates cognitive, affective, and somatic mechanisms that underlie SAD, let alone *taijin kyofusho.* The sparse literature that does exist emphasizes the role of repetitive negative thinking in general, and rumination in particular, in the maintenance of social anxiety symptoms. Individuals who experience high anxiety during social situations are likelier to engage in post-event rumination (58). Although rumination is a transdiagnostic and transcultural factor seen among many anxiety disorders and cultural groups, the content of rumination is unique for individuals who experience SAD. Typically, rumination in SAD is related to self-evaluations of one's performance in the situation. However, there is limited literature examining whether ruminating about one's anxiety symptoms in general can also impact post-event rumination following specific social situations.

A study sought to examine whether this general propensity to ruminate over one's anxiety symptoms and other established constructs, such as anxiety sensitivity, are associated with post-event rumination in SAD. This study on Canadian college students found that social anxiety and anxious rumination were significantly predictive of how much participants ruminated about the anxiety-provoking social event following the experience. Interestingly, anxiety sensitivity was not related to post-event rumination (59). These findings suggest that the cognitive mechanism of "thinking a lot" – specifically rumination-type thoughts – influences the maintenance of SAD symptoms. "Thinking a lot" can also be applied to future worries in SAD. For instance, individuals with SAD-like symptoms often report anticipatory anxiety for future social situations (60).

The maintenance of SAD via "thinking a lot" can be explained in three ways. First, when individuals engage in post-event rumination, they might sustain the

experience of dysphoria by dwelling upon their experience and strengthening their beliefs as socially inept individuals. Second, the aversive experiences associated with social interactions may lead individuals to avoid future social interactions. This avoidance is negatively reinforced by limiting the aversive consequences (e.g., dysphoria and rumination) in the short term but strengthening other aversive consequences in the long term (e.g., isolation). Third, anticipating negative evaluation is likely to increase state anxiety in a social situation, contributing to poorer social interactions and objectively negative evaluations by others. Thus, "thinking a lot" about future social interacts can inadvertently cause true negative outcomes, which can continue to negatively reinforce future avoidance behaviors.

While cognitive theories of SAD have been tested experimentally among Anglo-European or other Westernized populations, little literature examines the relevance of cognitive mechanisms among individuals who predominantly report *taijin kyofusho*. Experimental studies that test these hypotheses with diverse groups, including those with only *taijin kyofusho* and those with comorbid *taijin kyofusho* and SAD, can enhance the knowledge base on the transcultural applicability of cognitive theories of SAD.

Cultural Considerations for Generalized Anxiety Disorder (GAD) Across Cultures

Generalized anxiety disorder, as defined in the DSM 5, refers to a pattern of excessive worrying accompanied by irritability, muscle tension, and sleep and concentration difficulties that endure for over 6 months, cause distress or impairment, and are not attributable to other causes (e.g., substance withdrawal, medical condition, or another anxiety disorder) (12). The symptom profile of GAD can vary widely across cultures, such that some individuals may present with predominantly somatic symptoms, whereas others may have a mixed symptom profile. However, the putative hallmark symptom of GAD is excessive worry (6, 12).

The variability in symptom profile of GAD is documented across cultures. For example, one study elicited typical symptom presentations corresponding with anxiety from eight countries through descriptive interviews with psychiatrists in Asia, Latin America, North Africa, and Eastern Europe (42). Psychiatrists from India and Chile reported that clients presented with and subjectively complained of worry, tension, and "thinking a lot," which are considered characteristic of GAD as conceptualized by the DSM 5 (12). However, the vast majority of these cultural groups reported somatic symptoms that were treated as expressions of generalized dysphoria rather than concrete diagnostic entities that corresponded with DSM or ICD criteria. Somatic symptoms similar to those seen in GAD, yet expressed in unique idioms, included "heart rushing" (Brazil), "[going] to the bathroom frequently" (Peru), "cannot swallow" (Venezuela, Brazil), "something [blocking] the chest," and "heart stop" (Brazil, Peru, Morocco). Such differences in the symptom profile and the prominence of somatic discomfort during general anxiety warrant assess-

ment of transdiagnostic and transcultural processes. Such assessments may better explain cultural variations of GAD compared to symptom checklists that assess symptoms that do not have cross-cultural equivalence.

The centrality of "thinking a lot" is easily identified in the etiology and maintenance of GAD, given that excessive worry is an essential diagnostic marker of GAD. What is likely to differ between cultural groups are the worry domains. According to work conducted with Cambodian refugees, multiple worry domains include the following: finances for themselves and relatives in Cambodia, safety related to living in poor areas with ongoing violence, health concerns, catastrophic interpretations of somatic symptoms, and spiritual status of relatives who may be believed to be suffering because of culturally inappropriate burial due to missed opportunities for completing culturally indicated bereavement rites (61).

Aside from unique worry domains, Cambodians also attribute the consequences of worry in a culturally distinct manner. For instance, Cambodians have multiple concerns following a worry episode. Some examples of the feared impact of worry include the following: mental agitation, overheated and potentially damaged brain, and weakened mind and body. Further adverse consequences of worrying include poor memory, dizziness, propensity for *khyâl attacks,* cardiac arrest, stroke, and insanity (62). These feared consequences have emerged as linking factors between worry episodes and more severe psychopathology. Specifically, worry was associated with posttraumatic stress disorder (PTSD) as suggested by a path analysis study exploring mechanisms that explain feared consequences of *khyâl attacks* (61). This relationship between *khyâl attacks* and PTSD was explained by worry-induced somatic arousal, worry-induced catastrophic cognitions, worry-induced trauma recall, inability to stop worry, and irritability. Findings from this work suggest that all three transcultural and transdiagnostic mechanisms proposed in this chapter – i.e., "thinking a lot" (by way of worry and associated catastrophic cognitions), anxiety sensitivity (by way of worry-induced somatic arousal), and somatization (by way of discomfort from multiple interacting somatic sensations) – explained GAD-like symptoms and its association with more severe psychopathology such as PTSD.

A final consideration in conceptualizing GAD across cultures relates to the role of the socioeconomic and safety context a client is in. Specifically, it is essential to assess current stressors because they might be compounding worry and impacting the chronicity of its course. For cultural groups living in contexts of ongoing violence, poverty, or structural inequities, assessing worry as "excessive" (a qualifier needed to diagnose GAD) may be more difficult as their worry could be adaptive for addressing true safety threats.

Summary

The differential prevalence of anxiety disorders by cultural group suggests that differences in explanatory models, display rules, and certain key psychopathological mechanisms may alter the clinical presentation of anxiety across cultures. Cross-cultural

approaches to sensitively assessing and addressing anxiety disorders take into account local and universal factors known to shape anxiety. Considering local CCDs with transcultural and transdiagnostic targets can provide a holistic conceptualization of how anxiety is experienced and expressed in different cultural groups. In turn, these transcultural processes are profoundly shaped by the local culture. These approaches to understanding anxiety were illustrated in case examples from Cambodian refugees, Latin American immigrants, and Japanese and Korean individuals.

The literature reviewed highlights the importance of assessing for transdiagnostic and transcultural factors that have been linked with variable presentation of anxiety disorders across cultural groups. Cognitive processes, such as "thinking a lot," are promising constructs to assess as many anxiety disorders are theorized to have cognitive underpinnings. Relatedly, it is important to assess catastrophic cognitions that serve to maintain anxiety disorders. Anxiety sensitivity is a promising affective target for determining risk of developing anxiety disorders. Additionally, somatic presentations are commonly reported among diverse cultural groups, so assessing a broad set of somatic sensations, along with the interpretation of these sensations, can enable more comprehensive recognition of problems.

While this chapter has synthesized current literature on three major anxiety disorders, much more research is needed in diverse cultural groups to comprehensively account for differences across all the anxiety disorders. Mixed-methods research that accounts for DSM 5 criteria alongside local idioms and syndromes is especially warranted for accurate understanding of culturally unique symptom presentations. Another limitation of the literature reviewed is that several unique ethnic groups are collectively studied as belonging to one cultural group. However, it is often untenable to disaggregate the specific ethnic groups that constitute minority cultural groups due to challenges in acquiring sufficient sample sizes (23). Efforts to broaden research from comparative inquiries on specific ethnic groups to other understudied populations are needed.

References

1. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: A systematic review and meta-regression. Psychol Med [Internet]. 2013 [cited 2018 Nov 24];43;897–910. Available from: https://www.researchgate.net/publication/229064179
2. Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Arch Gen Psychiatry [Internet]. 2005 Feb 1. [cited 2018 Nov 27];62(2):182. Available from: http://archpsyc.jama-network.com/article.aspx?doi=https://doi.org/10.1001/archpsyc.62.2.182.
3. Asnaani A, Richey JA, Dimaite R, Hinton DE, Hofmann SG. A Cross-Ethnic Comparison of Lifetime Prevalence Rates of Anxiety Disorders.
4. Burnam MA, Hough RL, Karno M, Escobar JI, Telles CA. Acculturation and Lifetime Prevalence of Psychiatric Disorders Among Mexican Americans in Los Angeles. J Health Soc Behav [Internet]. 1987 Mar [cited 2018 Nov 29];28(1):89. Available from: http://www.jstor.org/stable/2137143?origin=crossref
5. Alegría M, Ph D, Canino G, Ph D, Shrout PE, et al. Prevalence of Mental Illness in Immigrant and Non-Immigrant U.S. Latino Groups. Am J Psychiatry [Internet]. 2003 [cited 2018 Nov

24];165(April):359–69. Available from: https://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.2007.07040704

6. Lewis-Fernández R, Hinton DE, Laria AJ, Patterson EH, Hofmann SG, Craske MG, et al. Culture and the anxiety disorders: recommendations for DSM-V. Depress Anxiety [Internet]. 2010 Feb. [cited 2018 Nov 30];27(2):212–229. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20037918

7. Snowden LR, Yamada A-M. Cultural Differences in Access to Care. Annu Rev Clin Psychol [Internet]. 2005 [cited 2018 Nov 30];1(1):143–66. Available from: http://www.sjsu.edu/people/edward.cohen/courses/c3/s1/snowden_cultural_differences.pdf

8. Merikangas KR, He JP, Burstein M, Swendsen J, Avenevoli S, Case B, et al. Service utilization for lifetime mental disorders in U.S. adolescents: results of the national comorbidity surveyAdolescent supplement (NCS-A). J Am Acad Child Adolesc Psychiatry [Internet]. 2011 Jan [cited 2018 Nov 24];50(1):32–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21156268

9. Kim G, Aguado Loi CX, Chiriboga DA, Jang Y, Parmelee P, Allen RS. Limited English proficiency as a barrier to mental health service use: A study of Latino and Asian immigrants with psychiatric disorders. J Psychiatr Res [Internet]. 2011 [cited 2018 Nov 24];45(1):104–10. Available from: https://s3.amazonaws.com/academia.edu.documents/43679583/Limited_English_proficiency_as_a_barrier20160313-2748-1f1mjf5.pdf?AWSAccessKeyId=AKIAIWOWYYGZ2Y53UL3A&Expires=1543085053&Signature=UyzCpAKo6tSHVEpZDrNjdab7LAI%253D&response-content-disposition=inline%25

10. Schouten BC, Meeuwesen L. Cultural differences in medical communication: a review of the literature. Patient Educ Couns. 2006;64:21–34.

11. Nichter M. Idioms of distress revisited. Cult Med Psychiatry. 2010;34(2):401–16.

12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub. 2013.

13. Lewis-Fernández R, Gorritz M, Raggio GA, Peláez C, Chen H, Guarnaccia PJ. Association of trauma-related disorders and dissociation with four idioms of distress among Latino psychiatric outpatients. Cult Med Psychiatry. 2010;34(2):219–43.

14. Salgado de Snyder VN, Diaz-Perez MJ, Ojeda VD. The Prevalence of Nervios and Associated Symptomatology Among Inhabitants of Mexican Rural Communities. Cult Med Psychiatry [Internet]. 2000 [cited 2018 Oct 9];24(4):453–70. Available from: http://link.springer.com/10.1023/A:1005655331794

15. Kohrt BA, Rasmussen A, Kaiser BN, Haroz EE, Maharjan SM, Mutamba BB, et al. Cultural concepts of distress and psychiatric disorders: literature review and research recommendations for global mental health epidemiology. Int J Epidemiol [Internet]. 2014. [cited 2018 Aug 23];43(2):365–406. Available from: https://pdfs.semanticscholar.org/e1b6/500c3ed5a4321c606b6c0bd1825459da0c7a.pdf

16. Hinton DE, Lewis-Fernández R. The cross-cultural validity of posttraumatic stress disorder: implications for DSM-5. Depress Anxiety [Internet]. 2011 Sep [cited 2014 Sep 9];28(9):783–801. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21910185

17. Kirmayer LJ. Cultural variations in the clinical presentation of depression and anxiety: implications for diagnosis and treatment. J Clin Psychiatry. 2001;62(suppl 13):22–30.

18. Raguram R, Weiss MG. Explanatory model interview catalogue (EMIC) for outpatient psychiatry problems and stigma. Instrument for collaborative research. National Institute of Mental Health and neuro sciences, Bangalore, India and Swiss tropical institute, Basel. 1997;(December).

19. Ekman P, Sorenson ER, Friesen W V. Pan-cultural elements in facial displays of emotion. Science [Internet]. 1969 Apr 4. [cited 2018 Nov 28];164(3875):86–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5773719

20. Leong FTL, Kalibatseva Z. Cross-cultural barriers to mental health services in the United States. Cerebrum [Internet]. 2011 Mar [cited 2018 Nov 30];2011:5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23447774

21. Kirmayer LJ, Sartorius N. Cultural models and somatic syndromes. Psychosom Med. 2007;69(9):832–40.
22. Kirmayer LJ, Young A. Culture and somatization: clinical, epidemiological, and ethnographic perspectives. Psychosom Med. 1988;60(4):420–30.
23. Leong FTL, Lau ASL, Rogler L, Malgady R, Rodriguez D. Barriers to providing effective mental health services to Asian Americans. Ment Health Serv Res [Internet]. 2001 [cited 2018 Nov 30];3. Available from: https://laulab.psych.ucla.edu/psych-laulab/wp-content/uploads/sites/2/2013/11/leong-lau-2001-mhsr.pdf.
24. Hinton DE, Lewis-Fernández R, Kirmayer LJ, Weiss MG. Illn Explanations. 2007:1980):1–16.
25. Hinton DE, Reis R, de Jong J. The "thinking a lot" idiom of distress and PTSD: an examination of their relationship among traumatized Cambodian refugees using the "thinking a lot" questionnaire. Med Anthropol Q. 2015;29(3):357–80.
26. Hinton DE, Hinton AL, Eng K-T, Choung S. PTSD and key somatic complaints and cultural syndromes among rural Cambodians: the results of a needs assessment survey. Med Anthropol Q [Internet]. 2012 Sep 16 .[cited 2014 Sep 24];26(3):383–407. Available from: http://doi.wiley.com/10.1111/j.1548-1387.2012.01224.x
27. Ehring T, Watkins ER. Repetitive negative thinking as a transdiagnostic process. Int J Cogn Ther [Internet]. 2008 [cited 2018 Dec 6];1(3):192–205. Available from: https://s3.amazonaws.com/academia.edu.documents/42533987/Repetitive_Negative_Thinking_as_a_Transd20160210-13040-vgtd2w.pdf?AWSAccessKeyId=AKIAIWOWYYGZ2Y53UL3A&Expires=15441-12116&Signature=hv2u7eu%2B4OECYz%2FDLDszEpvGylA%3D&response-content-disposition=inl
28. Hinton DE, Barlow DH, Reis R, de Jong J. A transcultural model of the centrality of "thinking a lot" in psychopathologies across the globe and the process of localization: a Cambodian refugee example. Vol. 40, Cult Med Psychiatry. Springer US; 2016. 570–619 p.
29. Kaiser BN, Haroz EE, Kohrt BA, Bolton PA, Bass JK, Hinton DE. "Thinking too much": a systematic review of a common idiom of distress. Soc Sci Med [Internet]. 2015;147:170–183. Available from: https://doi.org/10.1016/j.socscimed.2015.10.044
30. Hinton DE, Chhean D, Pich V, Safren SA, Hofmann SG, Pollack MH. A randomized controlled trial of cognitive-behavior therapy for Cambodian refugees with treatment-resistant PTSD and panic attacks: A cross-over design. J Trauma Stress [Internet]. 2005 [cited 2018 Oct 2];18(6):617–29. Available from: www.interscience.wiley.com
31. Hinton DE, Pich V, Safren SA, Pollack MH, McNally RJ. Anxiety sensitivity in traumatized Cambodian refugees: a discriminant function and factor analytic investigation. Behav Res Ther [Internet]. 2005;43(12):1631–1643. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16239155
32. Zvolensky MJ, McNeil DW, Porter CA, Stewart SH. Assessment of anxiety sensitivity in young American Indians and Alaska natives. Behav Res Ther [Internet]. 2001 Apr 1. [cited 2018 Nov 28];39(4):477–493. Available from: https://www.sciencedirect.com/science/article/pii/S0005796700000103
33. Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav Res Ther [Internet]. 1986 Jan 1 [cited 2018 Nov 29];24(1):1–8. Available from: https://www.sciencedirect.com/science/article/pii/0005796786901439
34. Capron DW, Kotov R, Schmidt NB. A cross-cultural replication of an interactive model of anxiety sensitivity relevant to suicide. Psychiatry Res [Internet]. 2013 Jan 30 [cited 2018 Nov 29];205(1–2):74–8. Available from: https://www.sciencedirect.com/science/article/pii/S0165178112004386
35. Zvolensky MJ, Arrindell WA, Taylor S, Bouvard M, Cox BJ, Stewart SH, et al. Anxiety sensitivity in six countries. Behav Res Ther [Internet]. Pergamon; 2003 [cited 2018 Nov 28];41:841–59. Available from: https://www.sciencedirect.com/science/article/pii/S0005796702001870
36. Varela RE, Weems CF, Berman SL, Hensley L, de Bernal MCR. Internalizing symptoms in Latinos: the role of anxiety sensitivity. J Youth Adolesc [Internet]. 2007 May 13 .[cited 2018 Nov 28];36(4):429–440. Available from: http://link.springer.com/10.1007/s10964-007-9168-4

37. Hinton DE, Chhean D, Fama JM, Pollack MH, McNally RJ. Gastrointestinal-focused panic attacks among Cambodian refugees: associated psychopathology, flashbacks, and catastrophic cognitions. J Anxiety Disord [Internet]. 2007 Jan 1 [cited 2018 Nov 28];21(1):42–58. Available from: https://www.sciencedirect.com/science/article/pii/S0887618506000466

38. Pina AA, Silverman WK. Clinical phenomenology, somatic symptoms, and distress in Hispanic/Latino and European American youths with anxiety disorders. J Clin Child Adolesc Psychol [Internet]. 2004 [cited 2018 Nov 28];33:227–36. Available from: http://www.tandfonline.com/doi/abs/10.1207/s15374424jccp3302_3

39. Lipowski ZJ. Z.J. Lipowski, M.D., F.R.C.P.(C). Am J Psychiatry [Internet]. 1988 [cited 2018 Nov 29];145(November):1358–68. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.469.4798&rep=rep1&type=pdf

40. Hoge EA, Tamrakar SM, Christian KM, Mahara N, Nepal MK, Pollack MH, et al. Cross-cultural differences in somatic presentation in patients with generalized anxiety disorder. J Nerv Ment Dis [Internet]. 2006 Dec [cited 2018 Nov 28];194(12):962–6. Available from: https://insights.ovid.com/crossref?an=00005053-200612000-00013

41. Escobar JI, Gureje O. Influence of Cultural and Social Factors on the Epidemiology of Idiopathic Somatic Complaints and Syndromes. Psychosom Med [Internet]. 2007 Nov [cited 2018 Dec 6];69(9):841–5. Available from: https://insights.ovid.com/crossref?an=00006842-200711000-00005

42. Halbreich U, Alarcon RD, Calil H, Douki S, Gaszner P, Jadresic E, et al. Culturally-sensitive complaints of depressions and anxieties in women. J Affect Disord [Internet]. 2007 Sep 1. [cited 2018 Dec 6];102(1–3):159–176. Available from: https://www.sciencedirect.com/science/article/pii/S0165032706004344

43. Dzokoto VA, Okazaki S. Happiness in the eye and the heart: somatic referencing in west African emotion lexica. J Black Psychol [Internet]. 2006 May 25 .[cited 2018 Dec 6];32(2):17–140. Available from: http://journals.sagepub.com/doi/10.1177/0095798406286799

44. Hinton DE, Hofmann SG, Rivera E, Otto MW, Pollack MH. Culturally adapted CBT (CA-CBT) for Latino women with treatment-resistant PTSD: a pilot study comparing CA-CBT to applied muscle relaxation. Behav Res Ther [Internet]. 2011 Apr 1 [cited 2018 Dec 1];49(4):275–80. Available from: https://www.sciencedirect.com/science/article/pii/S0005796711000222?via%3Dihub

45. Hinton DE, Kredlow MA, Bui E, Pollack MH, Hofmann SG. Treatment change of somatic symptoms and cultural syndromes among Cambodian refugees with PTSD. Depress Anxiety [Internet]. 2012 [cited 2018 Jul 22];29(2):147–54. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1002/da.20905

46. Hinton DE, Pollack MH. Introduction to the special issue: anxiety disorders in cross-cultural perspective. CNS Neurosci Ther. 2009;15(3):207–9.

47. Clark DM, Ehlers A. An overview of the cognitive theory and treatment of panic disorder. Appl Prev Psychol [Internet]. 1993 Jun1 [cited 2018 Nov 30];2(3):131–9. Available from: https://www.sciencedirect.com/science/article/pii/S0962184905801192

48. Lewis-Fernández R, Guarnaccia PJ, Martínez IE, Salmán E, Schmidt A, Liebowitz M. Comparative phenomenology of ataques de nervios, panic attacks, and panic disorder. Cult Med Psychiatry. 2002;26(2):199–223.

49. Hinton DE, Lewis-Fernández R, Pollack MH. A model of the generation of ataque de nervios: the role of fear of negative affect and fear of arousal symptoms. CNS Neurosci Ther. 2009;15(3):264–75.

50. Sullivan GM, Coplan JD, Kent JM, Gorman JM. The noradrenergic system in pathological anxiety: a focus on panic with relevance to generalized anxiety and phobias. Biol Psychiatry [Internet]. 1999 Nov 1. [cited 2019 Feb 14];46(9):1205–1218. Available from: https://www.sciencedirect.com/science/article/pii/S0006322399002462

51. Hinton DE, Patel A. Cultural adaptations of cognitive behavioral therapy. Psychiatr Clin North Am [Internet]. 2017 [cited 2018 Jul 31];40:701–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29080595

52. Wong QJJ, Rapee RM. The aetiology and maintenance of social anxiety disorder: a synthesis of complimentary theoretical models and formulation of a new integrated model. J Affect Disord [Internet]. 2016 Oct 1 [cited 2018 Dec 6];203:84–100. Available from: https://www.sciencedirect.com/science/article/pii/S016503271630430X

53. Caldwell-Harris CL, Ayçiçegi A. When personality and culture clash: The psychological distress of Allocentrics in an individualist culture and Idiocentrics in a collectivist culture. Transcult Psychiatry [Internet]. 2006 Sep 30 .[cited 2018 Dec 6];43(3):331–361. Available from: http://journals.sagepub.com/doi/10.1177/1363461506066982

54. Krieg A, Xu Y. Ethnic differences in social anxiety between individuals of Asian heritage and European heritage: a meta-analytic review. Asian Am J Psychol. 2015;6(1):66.

55. Heinrichs N, Rapee RM, Alden LA, Bögels S, Hofmann SG, Ja Oh K, et al. Cultural differences in perceived social norms and social anxiety. Behav Res Ther [Internet]. 2006 Aug 1 [cited 2018 Nov 28];44(8):1187–1197. Available from: https://www.sciencedirect.com/science/article/pii/S0005796705001944

56. Hofmann SG, Hinton DE. Cross-cultural aspects of anxiety disorders. Curr Psychiatry Rep [Internet]. Springer US; 2014 [cited 2018 Dec 6];16:450. Available from: http://link.springer.com/10.1007/s11920-014-0450-3

57. Hofmann SG, Anu Asnaani MA, Hinton DE. Cultural aspects in social anxiety and social anxiety disorder. Depress Anxiety [Internet]. NIH Public Access; 2010 [cited 2018 Dec 6];27;1117–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21132847

58. Mellings TMB, Alden LE. Cognitive processes in social anxiety: the effects of self-focus, rumination and anticipatory processing. Behav Res Ther [Internet]. 2000 Mar 1 [cited 2018 Dec 6];38(3):243–257. Available from: https://www.sciencedirect.com/science/article/pii/S0005796799000406

59. Kocovski NL, Rector NA. Predictors of post-event rumination related to social anxiety. Cogn Behav Ther. 2007;36(2):112–22.

60. Hofmann SG. Cognitive factors that maintain social anxiety disorder: a comprehensive model and its treatment implications. Cogn Behav Ther [Internet]. 2007 Dec [cited 2018 Dec 7];36(4):193–209. Available from: http://www.tandfonline.com/doi/abs/10.1080/16506070701421313

61. Hinton DE, Nickerson A, Bryant RA. Worry, worry attacks, and PTSD among Cambodian refugees: a path analysis investigation. Soc Sci Med [Internet]. 2011 Jun 1 [cited 2018 Dec 6];72(11):1817–1825. Available from: https://www.sciencedirect.com/science/article/pii/S0277953611002279

62. Hinton DE, Bui E. Cultural considerations in the anxiety and anxiety-related Disorders. In: Olatunji B, editor. Handbook of anxiety and related disorders: Cambridge University Press.

Chapter 5
Anxiety Comorbidities: Mood Disorders, Substance Use Disorders, and Chronic Medical Illness

Andrew H. Rogers, Sarah T. Wieman, and Amanda W. Baker

Anxiety disorders, including generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, and specific phobia, are characterized by excessive fear, anxiety, and associated behavioral consequences [1]. Estimates suggest anxiety disorders are among the most common psychiatric illnesses in the world, with between 4% and 25% of individuals suffering from one or more anxiety disorders in their lifetime [2]. Furthermore, current (12 month) prevalence rates in the United States hover near 11% [3]. There is considerable research suggesting that individuals with anxiety disorders also report comorbidities including other mental health concerns, substance use, and physical illness. A large body of epidemiological research suggests that a significant proportion of individuals with anxiety disorders also meet criteria for a mood disorder [4, 5] and alcohol or substance use disorders [3, 6]. More recent research exploring the prevalence rates of anxiety disorders among individuals with chronic disease (e.g., pain, diabetes, heart disease) suggests that individuals with chronic disease and anxiety disorders similarly report overall greater disease burden [7]. The cycle of these comorbidities contributing to greater anxiety and more severe comorbidity as well as the anxiety exacerbating the comorbidities in turn contributes to overall greater anxiety symptomology [8–10]. This suggests that there is a greater need to better understand

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anxiety and its comorbidities with mood, substance, and chronic medical disorders.

Not only do these comorbidities contribute to overall greater severity and disease burden, but these comorbidities also complicate treatment for anxiety and related conditions. Additionally, individuals with anxiety and a comorbid disorder report poor treatment outcomes than those with a single disorder [11], complicating treatment planning and execution. This chapter will review anxiety and its comorbidity with mood disorders, substance use disorders, and chronic medical conditions, with a focus on chronic pain, and will explore the epidemiology, mechanisms, clinical features, and treatments in greater depth.

Anxiety and Mood Disorders

Comorbidity of anxiety and mood disorder is quite common, with some research suggesting that as many as 60% of individuals with an anxiety disorder also meet criteria for major depressive disorder [12]. As noted above, individuals with both anxiety and mood disorders, compared to individuals with only one disorder, show greater functional impairment, lower quality of life, and poorer treatment outcomes. In the next section, we will briefly review comorbidity between mood disorders and anxiety disorders and discuss the impact of these comorbidities.

Epidemiology and Impact

The majority of existing work has primarily focused on the comorbid relationship between depression and the range of anxiety disorders. For instance, the National Comorbidity Survey-Replication (NCS-R) indicates that, among those with panic disorder (PD), upwards of 80% of individuals meet diagnostic criteria for another psychiatric disorder. About 35% of those individuals meet criteria for major depressive disorder (MDD), 14% for bipolar disorder, and 10% for dysthymia [12]. Similar rates of comorbidity have been observed among individuals with social anxiety disorder (SAD), where the NCS-R found that 37% of those individuals with SAD also met criteria for MDD [12]. The highest observed comorbidity between anxiety and mood exists between generalized anxiety disorder (GAD) and MDD, where upwards of 60% of individuals with GAD also met criteria for MDD [13, 14].

These high rates of anxiety/mood comorbidity are associated with a number of negative clinical outcomes such as suicidality and substance use. For instance, previous research among individuals with comorbid panic disorder and major depressive disorder found that suicide attempts were increased among this group compared to those with one disorder [15]. Additional research suggests that the rate of suicide attempts is more than double among individuals with comorbid PD and MDD com-

pared to those with only one disorder [16]. Similar cross-sectional and longitudinal results were found with SAD and MDD, where comorbid diagnosis of SAD and MDD in adolescence was associated with greater likelihood of later substance abuse and suicide attempt compared to those with only one disorder [17]. What's more, those with comorbid GAD and MDD reported more functional impairment than those with only one disorder [18].

These observed comorbidities have a significant impact on treatment response rates. Recent research found that having any anxiety disorder comorbidly with MDD was associated with a chronic and more severe course of treatment compared to those individuals with only anxiety disorders [19]. Examining specific anxiety disorders found that both comorbid SAD and MDD and comorbid GAD and MDD were associated with poorer response to treatment than individuals with a single disorder [20, 21].

Key Clinical Features

Although anxiety and mood disorders represent distinct diagnostic categories, there are a number of overlapping features of anxiety and mood disorders that complicate assessment and treatment planning. The most pertinent example of this is between GAD and MDD [22, 23]. Between these two disorders, there are some distinct symptom domains but also a number of overlapping symptoms, including irritability, restlessness, difficulty concentrating, trouble sleeping, and fatigue [1]. In clinical practice, however, these differences may be even more subtle. For instance, nausea associated with GAD may be associated with poor appetite, which is a symptom of MDD. Careful consideration of the presenting symptoms, diagnoses, and their overlap may be of critical importance to determine if an individual is presenting with GAD, MDD, or both.

Family and Genetics

Genome-wide association studies suggest that the heritability of psychiatric disorders is explained by large numbers of genes that each contribute a small increased risk for the development of certain disorders [24]. Therefore, genetic differences in isolation are not thought to cause psychiatric disorders but instead are thought to increase one's risk and vulnerability to the development of the disorder. A number of genetic risk factors have been identified to be shared across anxiety and depression, suggesting that this overlap in genetic susceptibility may contribute to the high rate of comorbidity among these classes of disorders [24, 25]. Therefore, inheriting certain genetic factors may make one more likely to develop anxiety as well as depression. Twin studies show support for a shared genetic vulnerability between anxiety and depression with some

genetic factors influencing general liability to initializing disorders (i.e., anxiety and mood disorders; [26, 27]). Additionally, family studies further support a shared genetic vulnerability between anxiety and depression. Offspring of parents with an anxiety disorder show an increased risk for developing a depressive disorder compared to offspring of nonpsychiatric controls, and offspring of parents with MDD show increased risk for developing an anxiety disorder [27–29]. These increased risks suggest a shared hereditable factor between anxiety and mood disorders.

Studies examining shared genetic risk factors between anxiety and mood disorders have identified several target genes including the Glutamate decarboxylase 1 gene and the catechol-O-methyltransferase (COMT) gene. These genes code for enzymes that help regulate the activity of a number of different neurotransmitters including gamma-aminobutyric acid (GABA), dopamine, epinephrine, and norepinephrine [30–32]. Overall, these genes have been associated with individual differences in trait neuroticism, reactivity and structural differences in the amygdala, and increased susceptibility across anxiety disorders and MDD ([25, 30, 31, 33]; Hettema et al. 2015). Meta-analyses examining variations of 5-HTTLPR, the promotor region of the serotonin transporter gene 5-HTT, have shown mixed and inconclusive results in their association with both anxiety and mood disorders (i.e., [34–36]). More recent research has focused on how shared genetic vulnerabilities may interact with shared environmental factors to increase one's risk for developing comorbid anxiety and depression.

Environmental Risk

In addition to genetic risk factors, certain environmental factors also increase susceptibility to anxiety and depression. As discussed previously, in a study of 1033 pairs of female twins, the nonfamilial environmental risk factors for anxiety and depression played an etiological role and showed modest overlap [23]. Furthermore, parenting behaviors, including parent rejection and control, have been linked to the intergenerational transmission of anxiety and depression [37]. Importantly, both anxious and depressed mothers show less warmth and more controlling parental behaviors [38]. Additionally, anxiety and depression are also associated with insecure attachment in early childhood [39].

Childhood trauma is thought to play a role in the development of anxiety and mood disorders. For example, emotional neglect in childhood is specifically associated with depressive disorder, dysthymia, and social phobia in adulthood [40]. Maladaptive emotion regulation strategies appear to mediate the relationship between childhood trauma and adulthood depression and anxiety symptoms [41]. Furthermore, additional research suggests that early life trauma interacts with genetic risk factors and increases the sensitivity of the neuroendocrine stress response system, putting individuals at heightened risk for anxiety and depression development following additional exposure to stress later in life [42–44].

Psychological stressors in adulthood, such as trauma or loss, are another environmental risk factor associated with both anxiety and depression.

Biomarkers

Anxiety and depression also show a number of shared biological markers that are thought to contribute to their development and high rates of comorbidity. The amygdala plays a role in emotional memory formation and retrieval [45]. Overactivation of the amygdala is evident in both anxiety and mood disorders [46–48]. Amygdala activation has been shown to decrease in response to successful treatment with antidepressants for depression and cognitive behavioral therapy for anxiety [45, 49]. The prefrontal cortex, which plays a role in emotional processing, is another brain region that has shown reliable dysregulation in anxiety and depression [45]. Prefrontal cortex dysfunction has been shown to be present during resting states as well as during emotional-cognitive tasks in anxious and depressed individuals [50]. Research also shows dysfunction in the connectivity between the prefrontal cortex and amygdala in depression and anxiety such that the prefrontal cortex does not show a compensatory increase in modulation in the presence of amygdala hyperactivity [51, 52]. This suggests possible impairment in top-down cognitive control over emotional responses in both anxiety and depression.

Findings have been mixed regarding brain-derived neurotrophic factor (BDNF) as a shared biomarker for anxiety and depression. Depressed individuals consistently show lower plasma and serum BDNF protein levels compared to healthy controls, and plasma BDNF levels normalize after antidepressant treatment [53, 54]. In contrast, studies of serum levels of BDNF in anxiety disorders have been somewhat inconsistent and suggest that lower BDNF protein levels are only seen in female individuals with anxiety disorders compared to female healthy controls [55]. While these findings are consistent with the preclinical literature that suggest gender plays a role in the association between BDNF and anxiety disorders, further research is warranted to better understand if BDNF is a shared biomarker for anxiety and mood disorders.

Cognitive and Personality Correlates

A number of different personality traits including neuroticism, anxiety sensitivity, and behavioral inhibition have been shown to play a role in both anxiety and depression, potentially contributing to their high comorbidity rate. Neuroticism is defined as a disposition to anxiety and emotional instability with a tendency to stay in negative mood states [56]. High scores of neuroticism are associated with increased risk for developing depression and anxiety [57, 58]. In a 10-year longitudinal study

examining neuroticism from adolescence to young adulthood, the group with higher absolute neuroticism levels showed a significant increased risk for developing depression and anxiety disorders compared to those with moderate neuroticism levels [59]. Furthermore, while scores of neuroticism are associated with depressive and anxiety disorder development in isolation, comorbid depression and anxiety show particularly high neuroticism [60]. In a 3-year longitudinal study of adolescents, Zinbarg et al. [61] found that neuroticism significantly predicted the onset of unipolar mood disorders and the onset of anxiety disorders. However, neuroticism most strongly predicted the onset of comorbid unipolar mood disorders and anxiety disorders [61].

Anxiety sensitivity, or the tendency to perceive anxious states as aversive or harmful [62], has also been shown to play a role in both anxiety and depression. Anxiety sensitivity has three components including fear of bodily sensations, fear of loss of cognitive control, and fear of publicly observable symptoms. The fear of loss of cognitive control shows strong, nonredundant associations with GAD, dimensional depression scores, and secondary diagnoses of MDD in a study of individuals with anxiety disorders with and without comorbid depression [63]. In a study on treatment-seeking individuals with anxiety and mood disorders, fear of publicly observable symptoms showed unique associations with SAD, GAD, and MDD, while fear of bodily sensations showed unique associations with SAD, PD, and specific phobia [64]. Additionally, both GAD and MDD are associated with low distress tolerance, or the ability to tolerate aversive emotional states, which may be another factor contributing to their high comorbidity [65].

Behavioral inhibition, a temperament characterized by the tendency to feel distress toward or withdrawn from unfamiliar situations, is another personality correlate of anxiety and depression, potentially contributing to their comorbidity. Behavioral inhibition is associated with both anxiety and depression in children and in young adults [66, 67]. Behavioral inhibition in childhood predicts later anxiety disorder development, with children remaining inhibited over timing being at the highest risk for anxiety disorders [68]. Furthermore, in a study examining the children of individuals with panic disorder, MDD, and comorbid PD and MDD, behavioral inhibition was more prevalent among the children of parents with comorbid MDD and PD than either disorder alone [69].

Anxiety and mood disorders have shown other common associations with personality traits. While negative affectivity seems to be a shared personality correlate across the anxiety and mood disorders, low positive affectivity has been linked to both depression and social anxiety disorder [22]. Furthermore, intolerance of uncertainty was originally thought to be a specific risk factor for GAD, but a meta-analysis by Gentes and Ruscio [70] found intolerance of uncertainty to show comparable associations to both GAD and MDD. Furthermore, anxiety and mood disorders have shown associations with low conscientiousness, and dysthymia disorder and social phobia, specifically, have been linked to low extraversion [71]. There are many overlapping cognitive and personality correlates for anxiety and mood disorders, which may contribute to the high comorbidity seen between these two classes of disorders. Furthermore, these cognitive and personality vulnerabilities are

thought to interact with both genetic and environmental factors, altogether contributing to an increased risk for comorbid anxiety and depression.

In summary, the onset of anxiety disorders often precedes the onset of mood disorders. The development of an anxiety disorder in childhood is associated with a two- to threefold increased risk for depression and anxiety disorders in adulthood [72]. Additionally, the presence of more than one anxiety disorder, severe impairment from an anxiety disorder, and comorbid panic attacks have all been associated with a significantly increased risk for developing MDD [73]. Furthermore, responding to anxiety symptoms with rumination and hopeless cognitions has also been associated with an increased risk for depressive symptom. Therefore, anxiety disorders and anxiety response styles may be additional risk factors for the development of depression, helping to account for their high comorbidity rate [73–75].

Treatment Considerations

A number of studies have examined best practices for treating these comorbidities, with some suggesting treating them sequentially and others suggesting treating them concurrently [11, 76, 77]. However, results are largely inconclusive, suggesting further research in the area must be conducted. Therefore, having a greater understanding of anxiety and its comorbidity with mood disorders, substance use disorders, and physical health problems is critical to ultimately improve assessment and treatment targets for this vulnerable population.

Existing treatments, including both pharmacotherapy and psychotherapy, have shown efficacy for treating anxiety and mood disorders alone. While these treatments do overlap, treating anxiety and mood disorders when they are comorbid may be associated with treatment complications. In terms of medications, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the first-line treatments for anxiety and mood disorders (see Chap. 13). Other medications, such as tricyclic antidepressants and monoamine oxidase inhibitors, are also treatment options, but are typically not used as first-line treatments due to their side effect profiles [5]. SSRIs and SNRIs have been shown to be effective for both the treatment of anxiety and mood disorders, but limited research suggests that dual-action drugs, such as SNRIs, may, in fact, be more effective for comorbid anxiety and mood disorders [78]. Some clinical guidelines suggest that, for individuals with comorbid anxiety and mood disorders, medications should be initiated at half the dose needed for the depressive symptoms because some individuals with anxiety may be hypersensitive to the initial effects of the antidepressants [79].

Psychotherapy, alone or in conjunction with pharmacotherapy, may also be particularly useful for individuals with comorbid anxiety and mood disorders. Cognitive behavioral therapy (CBT) is a well-established, efficacious treatment for anxiety and mood disorders, and research has consistently shown that CBT is more effective at reducing anxiety and depressive symptoms than waitlist control [80]. CBT works for both anxiety and mood disorders by challenging automatic negative thoughts,

exposing individuals to feared stimuli, and increasing engagement in pleasurable activities. However, despite the efficacy of CBT for anxiety and mood disorders individually, there still remains some debate as to the best way to treat these disorders when they appear comorbidly. One example of CBT that may be particularly useful for comorbid anxiety and mood disorders is the *Unified Protocol for Transdiagnostic Treatment of Emotional Disorders* [81, 82]. This treatment uses all of the established techniques of CBT, but instead of targeting the disorder itself, it targets the shared underlying vulnerability factors that are thought to maintain disorders. Given the considerable overlap between symptoms of anxiety and mood disorders, this approach may represent a more efficient and effective strategy for treating comorbid anxiety and mood disorders.

Mindfulness-based approaches, such as mindfulness-based stress reduction (MBSR; [83]), as well as acceptance and commitment therapy (ACT; [84]), may be additional efficacious strategies for the treatment of these comorbidities. Mindfulness-based treatments emphasize experiencing emotions nonjudgmentally and have been shown to be effective for anxiety and mood disorders individually; adapting these for individuals with comorbid anxiety and mood disorders may be important. ACT functions similarly, but targeting experiential avoidance and having individuals confront uncomfortable emotions head on, which is applicable to both anxiety and mood disorders.

Currently, pharmacotherapies, such as SSRIs and SNRIs, as well as psychotherapies such as CBT, are the first-line treatments for comorbid anxiety and mood disorders. However, novel strategies are currently being investigated that may augment or replace currently existing treatments. In terms of additional biological targets, ketamine, an NMDA agonist, has shown rapid and large effects for reducing anxiety and depressive symptoms among individuals with chronic mood and anxiety disorders [85]. Additionally, deep brain stimulation has been shown to reduce both depressive and anxiety symptoms among individuals with chronic, intractable depression [86]. Further, while research is highly limited, near-infrared light photobiomodulation has shown preliminary results to reduce both anxiety and depressive symptoms [87], yet rigorous randomized controlled trials are pending.

Additional novel strategies have focused on non-pharmacological interventions, some of which may prove useful as adjuncts to existing treatments. Specifically, brief computer-based interventions may be particularly useful. For example, attention bias modification (ABM) targets threat-related attention biases observed in anxiety and mood disorders that are often not targets in CBT [88]. Some preliminary work has shown the ABM reduced anxiety in a clinical population [89], but research has yet to determine if ABM is superior to pharmacotherapy or psychotherapy. More recent work has examined ABM as an adjunct to standard CBT for anxiety disorders, but studies examining these approaches have been met with mixed results. One study examining CBT plus attention bias training (compared to CBT with placebo) found overall reductions in anxiety symptoms, but these reductions did not differ by treatment group [90]. However, in a second similar study, but using a group CBT format, clinician-rated anxiety symptoms significantly reduced in the CBT + attention training group compared to placebo [91]. Along with attention, deficits in cognitive control have been similarly observed

among individuals with anxiety and mood disorders. Cognitive control has been shown to be a targetable and malleable factor in treatment [92], and some research among individuals with depression showed that targeting cognitive control reduced depressive symptoms [93]. However, no research has examined the impact of targeting cognitive control for individuals with comorbid anxiety and mood disorders.

Future Directions

Calling into question the diagnostic validity of the current diagnostic system (DSM-5), the high rates of comorbidity among mood and anxiety disorders suggest that they may be alternative clinical manifestations of the same underlying pathophysiological process instead of distinct entities [94, 95]. If etiological research stays within the constraints of the DSM-5 diagnostic categories, potentially important mechanistic overlaps between disorders could be overlooked [94]. Therefore, the National Institute of Mental Health has created the Research Domain Criteria (RDoC) initiative which aims to explore biological, neurological, and psychological etiological mechanisms that span current DSM-5 diagnoses [94, 96]. As RDoC research informs and transforms the classification of psychiatric disorders, changes to the classification system that are informed by etiological understanding may better account for the co-occurrence of mood and anxiety disorders [97]. Nevertheless, within the current diagnostic system, it remains important to identify comorbid anxiety and mood disorders within clinical practice [98]. This identification allows for appropriate treatment approaches to be taken in order to optimize outcomes.

Anxiety and Substance Use Disorders

Substance use disorders, encompassing ten substances including alcohol, caffeine, tobacco, cannabis, hallucinogens, opioids, inhalants, sedatives, and stimulants, are characterized by aberrant drug use patterns and associated negative consequences [1]. Like anxiety and mood disorders, the relationship between anxiety and substance use has been well documented in the literature. Estimates suggest that past 12-month prevalence rate of a substance use disorder alone was 9.35% and this diagnosis was significantly associated with anxiety disorder diagnoses [3]. Importantly, individuals with anxiety disorders with comorbid substance use reported overall greater anxiety severity, as well as more substance use problems compared to individuals without comorbid substance use [99]. As posited by the self-medication hypothesis, individuals use substances to ameliorate the elevated negative affect states associated with anxiety, which creates a negative feedback cycle whereby anxiety symptoms increase leading to more severe substance use [100]. This comorbidity, much like the comorbidity of anxiety and mood disorders, complicates assessment and treatment of both anxiety and substance use disorders.

Epidemiology and Impact

Given that substance use disorders are varied, the majority of research examining prevalence and incidence rates in the context of anxiety disorders has focused on substance use, and substance use disorders generally, rather than on particular classes of substance. A large body of work using the Netherlands Mental Health Survey and Incidence Study (NEMESIS) examined rates of substance use disorders occurring in the context of anxiety disorders and found that 10.5% of individuals with an anxiety disorder also met criteria for a substance use disorder [101]. Other studies have found that, among those with substance use disorders, upwards of 17% also meet criteria for any anxiety disorder [3]. Another related line of work has examined the comorbidity of anxiety disorders and substance use disorders among individuals with pre-existing mood disorders and found that these individuals may represent a distinct subgroup of individuals with mood disorders that may be particularly chronic and difficult to treat [102, 103].

Some research has documented elevated rates of substance use in the context of specific anxiety disorders. Social anxiety disorder has been consistently linked to elevated substance use, and theoretical models have postulated that coping motives (to cope with fears prior to and rumination after being embarrassed) are strongly associated with later substance use disorder diagnosis [100, 104]. While social anxiety disorder seems to have the most robust associations with substance use, panic disorder has also been associated with elevated substance use problems, with between 10 and 20% of individuals with panic disorder using substances to cope with elevated negative affect [105]. Less work has focused on the intersection of generalized anxiety disorder and substance use disorders, but of the work that does exist, similar patterns of increased use have been identified [106].

Substance use and substance use disorders in the context of anxiety disorders are clinically important, as they are associated with a host of negative outcomes greater than outcomes associated with any one disorder alone. Importantly, the comorbidity of anxiety and substance use disorders is associated with greater symptom severity and higher levels of disability [106, 107]. Consistent with the literature presented above, recovery from social anxiety was significantly slowed among individuals with comorbid alcohol and substance use disorders [108]. This pattern was also reflected among individuals with any anxiety disorder [109].

Key Clinical Features

Unlike anxiety and mood disorder comorbidity, there is less symptom overlap between anxiety disorders and substance use disorders. However, it is clinically important to recognize that anxiety and irritability may be a common symptom of substance use disorders, particularly when an individual may be in a phase of substance deprivation [1]. Despite the lack of symptom overlap, there is still considerable

comorbidity observed. Given this, understanding the function of substance use in the context of anxiety disorders may be particularly important in treatment planning and treatment success. One avenue that has recently garnered attention is substance use motives and expectancies. Typically, individuals that report using substances to cope with increased negative affect, as well as those expecting substance use to reduce negative affect, have the poorest prognosis [110]. Therefore, collecting information as to the function of substance use may be important.

Considerable work has been dedicated to understanding the temporal relations that exist between anxiety disorders and substance use disorders. A large longitudinal study found that baseline anxiety disorders were associated with later development of substance use disorders, but baseline substance use disorders were not associated with the later development of anxiety disorders [111]. Other work has found associations with early substance use disorders and later anxiety disorders but also found that neuroticism (general tendency to experience negative affect) in the context of substance use disorders was associated with later anxiety disorders [101]. Importantly, a number of individual difference factors have been found to be associated with the transition from anxiety disorders alone to anxiety comorbid with substance use disorders. Specifically, female gender, younger age, lower education, and unemployment were all associated with increased rates of anxiety occurring comorbidly with substance use disorders [112]. Other research also suggests that a history of childhood trauma and stressful events, as well as functional disability, may be associated with this transition [101]. These temporal findings highlight the importance of a thorough assessment of anxiety and related conditions early in life to identify those at highest risk for developing a later substance use disorder.

Family and Genetics

Few studies have examined family and genetic collective risk factors for anxiety and comorbid substance use disorders. It has been shown that there exists, albeit small in magnitude, overlap in genetic factors between anxiety and substance use disorders [113]. Yet some early research does suggest, however, that family transmission of these comorbid disorders can be best accounted for by shared, underlying vulnerability factors [114, 115]. Therefore, to best understand family and genetic risk factors for comorbid anxiety and substance use disorders, it is important to examine the family and genetic underpinnings of shared vulnerability factors. For instance, dysphoria and "acting out" behaviors have been shown to be independently associated with anxiety and substance use disorders, and these features have been shown to be transmitted generationally with moderate specificity [115]. However, one risk factor that has been consistently shown to confer heightened risk for both anxiety and substance use disorders is impulsivity [116].

Impulsivity has been shown to be an important feature of anxiety disorders [117] and substance use disorders [118], independently. Initial research has identified that *HTR2B stop codon gene to be present in a number of animals and humans displaying*

impulsive behavior [119]. *Additionally, twin studies examining heritability of impulsivity using a delay discounting impulsivity task found that there was significant heritability in task performance* (up to 62%; [120]).

Environmental Risk

Certain environmental risk factors have been identified as unique contributors to the development of comorbid anxiety and substance use disorders. A large body of work has focused on stressors occurring during childhood. One factor with consistent associations to anxiety and substance use disorders is childhood sexual abuse [121]. Research found that more severe forms of childhood sexual abuse were associated with a greater collective risk for developing psychiatric disorders, with an emphasis on anxiety and substance use disorders. Importantly, childhood sexual abuse was found to be associated with heightened risk after controlling for parental psychopathology and other family background characteristics.

Additional studies among women found that parental loss may, in fact, be a unique stressor associated with increased risk of psychopathology [122]. While all types of loss were associated with an increase in anxiety symptoms and disorders, the act of being separated from a parent was associated with both anxiety and alcohol problems. Importantly, this particular study documented that parental loss could account for up to 5% of variance in psychopathology outcomes and could account for up to 20% of shared psychiatric disorders between siblings. It is clear that the relationship and subsequent loss of a parent may be integral to better understanding shared vulnerabilities for anxiety and substance use disorders.

Similarly, parenting style has also been associated with greater risk for comorbid anxiety and substance use disorders. Specifically, coldness and authoritarian styles of parenting were found to be associated with anxiety and substance use disorders [123]. What's more, when examined concurrently, coldness was uniquely associated with anxiety and substance use disorders, and these associations did not differ between mother and father. However, the relationship between parenting style, anxiety, and substance use disorders was determined to be in a direction. Specifically, the relationship between parenting style (coldness) and substance use disorders was largely mediated by anxiety symptoms and disorders.

Cognitive and Personality Correlates

Given the dearth of research examining the comorbidity of anxiety and substance use disorders, little research has identified cognitive and personality correlates specifically associated with anxiety and substance use comorbidity. However, there are a number of risk factors that have been identified to be individually associated with each of these disorders, and therefore, there may be utility in reviewing them here

for future research. Some of these cognitive and personality factors that have been associated with anxiety and substance use disorders are neuroticism, anxiety sensitivity, and distress tolerance.

Neuroticism is a stable individual difference factor associated with psychiatric disorders. Most commonly, neuroticism has been associated with anxiety symptoms and disorders [124]. However, more recent research has linked neuroticism to substance use disorders as well [71, 112]. Importantly, in the referenced studies, neuroticism was examined as a predictor of these disorders in the context of other personality traits, and it was consistently found to be the strongest predictor of all disorders.

Anxiety sensitivity is another individual difference factor that has been associated with anxiety and substance use disorders. The majority of work examining anxiety sensitivity on anxiety substance use comorbidity has focused on cigarette smoking. Overall, anxiety sensitivity has been found to be a putative risk factor for smoking and problems associated with smoking in the context of anxiety [125, 126]. More specifically, anxiety sensitivity has been associated with negative affect-related smoking cognitions, suggesting that anxiety sensitivity is associated with an increased belief that smoking will decrease negative affect associated with anxiety. Some other work has examined anxiety sensitivity in the context of anxiety and marijuana use, and anxiety sensitivity was similarly associated with using marijuana to cope with negative emotions [127].

Finally, distress tolerance, or the ability to withstand negative psychological states [128], has been linked to anxiety and substance use comorbidity. A large review of the literature found distress tolerance to be associated with all psychopathology [129]. Looking more specifically, some research has identified distress tolerance to be associated with both anxiety symptoms and substance use problems, but the strength of these associations differed by demographic characteristics [130]. Additionally, similar to anxiety sensitivity, distress tolerance was found to be specifically associated with marijuana coping motives [127]. Overall, it is likely that distress tolerance is a putative risk factor for anxiety substance use comorbidity, and future research should examine how distress tolerance is associated with the temporal relationships between anxiety and substance use.

Treatment Considerations and Future Directions

Treatment for comorbid disorders generally presents numerous challenges due to the more severe and chronic nature of all disorders, but the intersection of anxiety and substance use disorders seems to present a particularly difficult clinical profile to treat. There is also considerable debate as to the best strategy to treat these co-occurring disorders. Some clinical theoretical orientations believe it is important to achieve abstinence from a substance prior to initiating treatment for anxiety disorders, while others believe in treating them concurrently [131]. Various strategies, including pharmacotherapy and psychotherapy, have proven useful for these

comorbid conditions. Additionally, novel treatment research has begun to identify new and innovative ways to reduce the overall disease burden associated with anxiety and substance use comorbidity.

Pharmacotherapies have shown efficacy for comorbid anxiety and substance use disorders, but particular treatment recommendations should be considered prior to initiating treatment with medication in this population [132]. First, it is important to acknowledge that individuals with substance use disorders may be more likely to abuse prescription medication. Additionally, substance use disorders have been found to be one of the biggest contributors to medication noncompliance, which is a significant concern in the context of anxiety disorders [133]. However, there have been studies examining the efficacy of pharmacotherapies for comorbid anxiety and substance use disorders, with the greatest body of research focusing on alcohol use disorder in the context of anxiety disorders. Of the studies reviewed [132], SSRIs have been shown to be safe and effective for treating anxiety disorders in the context of substance use disorders, and some studies have even shown that these medications may also reduce alcohol use. Importantly, research and clinical guidelines consistently state the benzodiazepines should be explicitly avoided for individuals with comorbid anxiety and substance use disorders due to high abuse potential for these medications.

It is also important to note that, in some cases, pharmacotherapy may be required, depending on the nature and severity of the substance use disorders [131]. Particularly in the case of alcohol use disorder and opioid use disorder, current clinical guidelines require the use of pharmacotherapies to prevent the medically dangerous symptoms associated with substance withdrawal. Oftentimes, benzodiazepines are used for individuals with alcohol use disorder and medication-assisted treatments such as methadone or buprenorphine are used for individuals with opioid use disorders. Particularly in these high-risk cases, integrated care from a medical doctor as well as a mental health clinician may be warranted to improve the clinical outcomes.

Psychotherapies have also had mixed results treating these comorbid disorders [107]. In individuals with comorbid anxiety and substance use disorders, targeting anxiety alone reduced anxiety symptoms but had little effect on substance use outcomes [134]. The same was found with treatment targeting substance use but not anxiety improving the substance use outcomes but not the anxiety. Given this lack of generalization, more recent research has focused on developing and implementing integrated treatments for anxiety and substance use disorders comorbidly. While still in their infancy, one treatment examining an integrated CBT protocol for anxiety and substance use disorders, compared to a treatment for anxiety alone, showed comparable reductions in anxiety and greater reductions in substance use behaviors [135]. Importantly, while a number of these treatments are still being developed and tested, integrated treatments seem to be the most effective for comorbid anxiety and substance use disorders. Further, and perhaps the most important, is that targeting one disorder in the context of another is *not* associated with worse outcomes for the other disorder [107]. This is particularly

important as the field moves to develop more efficacious treatments for all psychiatric disorders that occur alone or comorbid with other disorders.

Anxiety and Chronic Pain

A large body of work suggests that the co-occurrence of psychiatric disorders and chronic medical illness is associated with longer and more severe course of anxiety disorder as well as medical illness. The majority of early work focused on the relationship between depression and chronic medical illness, but more recent work has found anxiety to be equally, if not more, important to understand in the context of chronic medical illness [136, 137]. One particular chronic illness that has garnered recent attention is chronic pain, which is defined as persistent pain lasting for at least 3 months [138]. Emerging evidence highlights the importance and clinical relevance of understanding the relationship between anxiety symptoms and disorders in the context of chronic pain. Importantly, chronic pain is a highly debilitating condition associated with increased medical costs and decreased productivity [139], and these problems are exacerbated by anxiety disorders.

Epidemiology and Impact

Studies have examined prevalence rates of anxiety disorders in the context of chronic pain. Across studies, prevalence rates of anxiety disorders varied but, in general, showed consistently elevated rates. Studies using DSM-III diagnostic criteria and mixed chronic pain patients found that anywhere between 7.0% and 19.0% of individuals met criteria for an anxiety disorder [140–142]. Importantly, for studies using samples of only individuals with chronic lower back pain, rates of anxiety disorders were significantly higher, ranging from 17.0% to 28.8% of individuals [143–145]. More recent investigations using DSM-IV diagnostic criteria found similar elevations for anxiety disorders, where 17% of individuals with chronic pain met criteria for an anxiety disorder [146]. Some studies have also examined anxiety symptoms and found similar patterns whereby symptoms of anxiety were common and elevated among individuals with chronic pain [147].

Research has begun to understand how anxiety impacts the course of illness of individuals with chronic pain. A number of studies have examined the impact of anxiety in the context of chronic pain, compared to pain without anxiety, and found that those with anxiety reported the greatest pain severity as well as greatest disability due to pain [148]. Additionally, other research found that one anxiety disorder in the context of chronic pain was not associated with change in outcome, but multiple anxiety disorders in the context of chronic pain were associated with increased pain disability [149]. One mechanism hypothesized for these observed

increases is that anxiety interferes with an individuals' ability to cope with their pain, therefore exacerbating pain severity as well as negative consequences associated with pain, such as disability [150].

Key Clinical Features

Anxiety and chronic pain are common and often occur together, warranting particular clinical attention. When anxiety is overlooked in the context of chronic pain, treating the chronic pain is significantly more complicated, as it is often more severe and intractable [151]. Importantly, this relationship was also true in the other direction, where individuals receiving treatment for anxiety had poor outcomes if they had untreated and severe pain [141]. Importantly, assessment of pain in the context of anxiety requires detailed attention to pain severity, pain-related disability, attitudes about pain, and pain coping [138].

Another relevant clinical construct in these relationships is pain-related anxiety, defined as the fear of pain or pain-eliciting sensations [152]. More recent work examining the clinical impact of pain-related anxiety in the context of chronic pain has found that this particular anxiety is associated with a host of negative outcomes, including opioid misuse [153]. Pain-related anxiety has also been associated with onset and maintenance of other substance use relevant to pain (i.e., tobacco; [154]) and therefore may be a putative risk factor for poor outcomes in chronic pain. While not explicitly an anxiety disorder, more research is understanding the clinical impact of pain-related anxiety in the context of chronic pain. Pain-related anxiety may account for the significant disability observed for individuals with chronic pain. Assessment of pain-related anxiety may also be warranted to improve outcomes.

Treatment Considerations and Future Directions

Compared to anxiety and mood disorders and anxiety and substance use disorders, significantly less research has been done on treatment for comorbid anxiety and chronic pain. The majority of the existing work has examined psychotherapy for the treatment of comorbid anxiety and chronic pain, but only a small amount of work has examined pharmacotherapy in this context. This work generally concludes that medications may be useful when combined with psychotherapy. However, some emerging research with medications finds that some medications do, in fact, have properties that may be helpful for individuals with comorbid chronic pain and anxiety. For example, some research has shown the propranolol, which is classified as a beta-blocker, has analgesic properties as well as mechanisms that erase fear conditioning [155]. Additionally, gabapentin has been found to have analgesic and anxio-

lytic properties [156], making it particularly suitable to treat these comorbid conditions. Importantly, SSRIs have not proven useful for symptoms of chronic pain [157], but it is important to note that there have been no direct tests of SSRIs targeting symptoms of chronic pain.

Psychotherapy for the treatment of comorbid anxiety and chronic pain may also be an efficacious treatment strategy. A number of treatments with known efficacy for anxiety disorders, such as cognitive behavior therapy (CBT) and acceptance and commitment therapy (ACT), have shown efficacy for chronic pain conditions and may be particularly important for those suffering from both anxiety and chronic pain. Specifically, a meta-analysis examining the efficacy of CBT for chronic pain found that CBT was better than waitlist control for improving pain-related outcomes [158], but did not show improvements with mood-related outcomes. A more recent meta-analysis did find, however, that CBT did improve mood and pain outcomes among individuals with chronic pain [159], but the majority of these studies were only able to report on data immediately following treatment completion and not follow-up, and the majority compared CBT to a waitlist control prohibiting true causal claims to be made. A number of studies examining ACT for chronic pain have found more robust effects for both chronic pain and mood and anxiety symptoms [160]. A comparison study between CBT and ACT found that both treatments showed good effects for both pain and anxiety outcomes but found that patients reported higher satisfaction levels with ACT than with CBT [161]. Given this body of evidence, it suggests that while both CBT and ACT may be efficacious for chronic pain and anxiety, ACT may be preferred by patients.

Another nascent yet promising psychotherapy is graded pain exposure for the treatment of pain-related fear [162]. While still in its infancy, this treatment, structured much like exposure therapy for anxiety disorders (i.e., building a fear hierarchy), has been shown to reduce both subjective pain and pain-related fear and anxiety. However, to date little research has tested graded pain exposure in a rigorous randomized controlled design, so conclusions on the efficacy of this treatment, compared to existing efficacious treatments, must be interpreted with caution.

Conclusion

Anxiety disorders are highly comorbid with many mental and physical health conditions, including depression, substance use, and chronic pain. A large body of work supports the bidirectional relationship that anxiety had with each of these conditions, complicating treating and extending the longevity of the disorder. While progress has been made addressing anxiety disorders from a holistic, comorbidity perspective, much work in this area still needs to be done to improve treatments and reduce human suffering.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington: American Psychiatric Association; 2013.
2. Remes O, Brayne C, van der Linde R, Lafortune L. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. Brain Behav. 2016;6(7):e00497. https://doi.org/10.1002/brb3.497.
3. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on alcohol and related conditions. Arch Gen Psychiatry. 2004;61(8):807–16. https://doi.org/10.1001/archpsyc.61.8.807.
4. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse: results from the epidemiologic catchment area (ECA) study. JAMA. 1990;264(19):2511–8. https://doi.org/10.1001/jama.1990.03450190043026.
5. Wittchen H-U, Kessler RC, Beesdo K, Krause P, Höfler M, Hoyer J. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry. 2002;63(Suppl 8):24–34.
6. Lai HMX, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: a systematic review and meta-analysis. Drug Alcohol Depend. 2015;154:1–13. https://doi.org/10.1016/j.drugalcdep.2015.05.031.
7. DeJean D, Giacomini M, Vanstone M, Brundisini F. Patient experiences of depression and anxiety with chronic disease. Ont Health Technol Assess Ser. 2013;13(16):1–33.
8. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. Chest. 2013;144(3):766–77. https://doi.org/10.1378/chest.12-1911.
9. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. Clin Psychol Rev. 2000;20(2):149–71. https://doi.org/10.1016/S0272-7358(99)00027-6.
10. Myrick H, Brady K. Current review of the comorbidity of affective, anxiety, and substance use disorders. Curr Opin Psychiatry. 2003;16(3):261. https://doi.org/10.1097/01.yco.0000069080.26384.d8.
11. Coplan JD, Aaronson CJ, Panthangi V, Kim Y. Treating comorbid anxiety and depression: psychosocial and pharmacological approaches. World J Psychiatry. 2015;5(4):366–78. https://doi.org/10.5498/wjp.v5.i4.366.
12. Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2006;63(4):415–24. https://doi.org/10.1001/archpsyc.63.4.415.
13. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51(1):8–19.
14. Kessler RC, Wang PS. The descriptive epidemiology of commonly occurring mental disorders in the United States. Annu Rev Public Health. 2008;29:115–29. https://doi.org/10.1146/annurev.publhealth.29.020907.090847.
15. Goodwin RD, Roy-Byrne P. Panic and suicidal ideation and suicide attempts: results from the National Comorbidity Survey. Depress Anxiety. 2006;23(3):124–32. https://doi.org/10.1002/da.20151.
16. Goodwin R, Hamilton SP. Cigarette smoking and panic: the role of neuroticism. Am J Psychiatr. 2002;159(7):1208–13. https://doi.org/10.1176/appi.ajp.159.7.1208.
17. Stein MB, Fuetsch M, Müller N, Höfler M, Lieb R, Wittchen HU. Social anxiety disorder and the risk of depression: a prospective community study of adolescents and young adults. Arch Gen Psychiatry. 2001;58(3):251–6.

18. Wittchen H-U. Generalized anxiety disorder: prevalence, burden, and cost to society. Depress Anxiety. 2002;16(4):162–71. https://doi.org/10.1002/da.10065.

19. Batelaan NM, Rhebergen D, Spinhoven P, van Balkom AJ, Penninx BWJH. Two-year course trajectories of anxiety disorders: do DSM classifications matter? J Clin Psychiatry. 2014;75(9):985–93. https://doi.org/10.4088/JCP.13m08837.

20. Magee WJ, Eaton WW, Wittchen HU, McGonagle KA, Kessler RC. Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. Arch Gen Psychiatry. 1996;53(2):159–68.

21. Newman MG, Przeworski A, Fisher AJ, Borkovec TD. Diagnostic comorbidity in adults with generalized anxiety disorder: impact of comorbidity on psychotherapy outcome and impact of psychotherapy on comorbid diagnoses. Behav Ther. 2010;41(1):59–72. https://doi.org/10.1016/j.beth.2008.12.005.

22. Brown TA, Chorpita BF, Barlow DH. Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. J Abnorm Psychol. 1998;107(2):179–92.

23. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Major depression and generalized anxiety disorder: same genes, (partly) different environments? Arch Gen Psychiatry. 1992b;49(9):716–22. https://doi.org/10.1001/archpsyc.1992.01820090044008.

24. Demirkan A, Penninx BWJH, Hek K, Wray NR, Amin N, Aulchenko YS, van Dyck R, de Geus EJC, Hofman A, Uitterlinden AG, Hottenga J-J, Nolen WA, Oostra BA, Sullivan PF, Willemsen G, Zitman FG, Tiemeier H, Janssens ACJW, Boomsma DI, van Duijn CM, Middeldorp CM. Genetic risk profiles for depression and anxiety in adult and elderly cohorts. Mol Psychiatry. 2011;16(7):773–83. https://doi.org/10.1038/mp.2010.65.

25. Hettema JM. The nosologic relationship between generalized anxiety disorder and major depression. Depress Anxiety. 2008;25(4):300–16. https://doi.org/10.1002/da.20491.

26. Kendler KS, Aggen SH, Neale MC. Evidence for multiple genetic factors underlying DSM-IV criteria for major depression. JAMA Psychiat. 2013;70(6):599–607. https://doi.org/10.1001/jamapsychiatry.2013.751.

27. Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology. 2016;41(1):297–319. https://doi.org/10.1038/npp.2015.266.

28. Micco JA, Henin A, Mick E, Kim S, Hopkins CA, Biederman J, Hirshfeld-Becker DR. Anxiety and depressive disorders in offspring at high risk for anxiety: a meta-analysis. J Anxiety Disord. 2009;23(8):1158–64. https://doi.org/10.1016/j.janxdis.2009.07.021.

29. Smoller JW. Disorders and borders: psychiatric genetics and nosology. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(7):559–78. https://doi.org/10.1002/ajmg.b.32174.

30. Donner J, Sipilä T, Ripatti S, Kananen L, Chen X, Kendler KS, et al. Support for involvement of glutamate decarboxylase 1 and neuropeptide Y in anxiety susceptibility. Am J Med Genet B Neuropsychiatr Genet. 2012;159B:316–27.

31. Hettema JM, An SS, Neale MC, Bukszar J, van den Oord EJCG, Kendler KS, et al. Association between glutamic acid decarboxylase genes and anxiety disorders, major depression, and neuroticism. Mol Psychiatry. 2006;11:752.

32. Smolka MN, Schumann G, Wrase J, Grüsser SM, Flor H, Mann K, et al. Catechol-O-methyltransferase val158met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. J Neurosci. 2005;25:836–42.

33. Domschke K, Dannlowski U. Imaging genetics of anxiety disorders. NeuroImage. 2010;53:822–31.

34. Bastiaansen JA, Servaas MN, Marsman JBC, Ormel J, Nolte IM, Riese H, Aleman A. Filling the gap: relationship between the serotonin-transporter-linked polymorphic region and amygdala activation. Psychol Sci. 2014;25(11):2058–66. https://doi.org/10.1177/0956797614548877.

35. Howe AS, Buttenschøn HN, Bani-Fatemi A, Maron E, Otowa T, Erhardt A, Binder EB, Gregersen NO, Mors O, Woldbye DP, Domschke K, Reif A, Shlik J, Kõks S, Kawamura Y, Miyashita A, Kuwano R, Tokunaga K, Tanii H, Smoller JW, Sasaki T, Koszycki D, De Luca V. Candidate genes in panic disorder: meta-analyses of 23 common variants in major anxiogenic pathways. Mol Psychiatry. 2016;21(5):665–79. https://doi.org/10.1038/mp.2015.138.

36. Munafò MR, Brown SM, Hariri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. Biol Psychiatry. 2008;63(9):852–7. https://doi.org/10.1016/j.biopsych.2007.08.016.

37. McLeod BD, Weisz JR, Wood JJ. Examining the association between parenting and childhood depression: a meta-analysis. Clin Psychol Rev. 2007;27(8):986–1003. https://doi.org/10.1016/j.cpr.2007.03.001.

38. Lovejoy MC, Graczyk PA, O'Hare E, Neuman G. Maternal depression and parenting behavior: a meta-analytic review. Clin Psychol Rev. 2000;20(5):561–92.

39. Davila J, Ramsay M, Stroud CB, Steinberg SJ. Attachment as vulnerability to the development of psychopathology. In: Development of psychopathology: a vulnerability-stress perspective; 2005. p. 215–42. https://doi.org/10.4135/9781452231655.

40. Spinhoven P, Elzinga BM, Hovens JGFM, Roelofs K, Zitman FG, van Oppen P, Penninx BWJH. The specificity of childhood adversities and negative life events across the life span to anxiety and depressive disorders. J Affect Disord. 2010;126(1–2):103–12. https://doi.org/10.1016/j.jad.2010.02.132.

41. Huh HJ, Kim KH, Lee H-K, Chae J-H. The relationship between childhood trauma and the severity of adulthood depression and anxiety symptoms in a clinical sample: the mediating role of cognitive emotion regulation strategies. J Affect Disord. 2017;213:44–50. https://doi.org/10.1016/j.jad.2017.02.009.

42. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001;49(12):1023–39.

43. Penza KM, Heim C, Nemeroff CB. Neurobiological effects of childhood abuse: implications for the pathophysiology of depression and anxiety. Arch Womens Ment Health. 2003;6(1):15–22. https://doi.org/10.1007/s00737-002-0159-x.

44. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA. 2009;301(21):2252–9. https://doi.org/10.1001/jama.2009.754.

45. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci. 2007;10(9):1116–24. https://doi.org/10.1038/nn1944.

46. Beesdo K, Lau JYF, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, Fromm SJ, Goldwin MA, Wittchen HU, Leibenluft E, Ernst M, Pine DS. Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch Gen Psychiatry. 2009;66(3):275–85. https://doi.org/10.1001/archgenpsychiatry.2008.545.

47. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007;164(10):1476–88. https://doi.org/10.1176/appi.ajp.2007.07030504.

48. Frodl TS, Koutsouleris N, Bottlender R, Born C, Jäger M, Scupin I, et al. Depression-related variation in brain morphology over 3 years: effects of stress? Arch Gen Psychiatry. 2008;65(10):1156–65.

49. Godlewska BR, Norbury R, Selvaraj S, Cowen PJ, Harmer CJ. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. Psychol Med. 2012;42(12):2609–17. https://doi.org/10.1017/S0033291712000591.

50. Messina I, Sambin M, Palmieri A, Viviani R. Neural correlates of psychotherapy in anxiety and depression: a meta-analysis. PLoS One. 2013;8(9):e74657. https://doi.org/10.1371/journal.pone.0074657.

51. Fales CL, Barch DM, Rundle MM, Mintun MA, Snyder AZ, Cohen JD, Mathews J, Sheline YI. Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. Biol Psychiatry. 2008;63(4):377–84. https://doi.org/10.1016/j.biopsych.2007.06.012.

52. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, Chen G, McClure-Tone EB, Ernst M, Pine DS. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry. 2008;65(5):568–76. https://doi.org/10.1001/archpsyc.65.5.568.

53. Bocchio-Chiavetto L, Bagnardi V, Zanardini R, Molteni R, Nielsen MG, Placentino A, Giovannini C, Rillosi L, Ventriglia M, Riva MA, Gennarelli M. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. World J Biol Psychiatry. 2010;11(6):763–73. https://doi.org/10.3109/15622971003611319.

54. Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol. 2008;11(8):1169–80. https://doi.org/10.1017/S1461145708009309.

55. Molendijk ML, Bus BA, Spinhoven P, Penninx BWJH, Kenis G, Prickaerts J, Voshaar RC, Elzinga BM. Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment. Mol Psychiatry. 2011;16(11):1088–95. https://doi.org/10.1038/mp.2010.98.

56. Enns MW, Cox BJ. Personality dimensions and depression: review and commentary. Can J Psychol. Revue Canadienne De Psychiatrie. 1997;42(3):274–84. https://doi.org/10.1177/070674379704200305.

57. Hettema JM, Prescott CA, Kendler KS. Genetic and environmental sources of covariation between generalized anxiety disorder and neuroticism. Am J Psychiatry. 2004;161(9):1581–7. https://doi.org/10.1176/appi.ajp.161.9.1581.

58. Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in women. Am J Psychiatry. 2002;159(7):1133–45. https://doi.org/10.1176/appi.ajp.159.7.1133.

59. Aldinger M, Stopsack M, Ulrich I, Appel K, Reinelt E, Wolff S, Grabe HJ, Lang S, Barnow S. Neuroticism developmental courses – implications for depression, anxiety and everyday emotional experience; a prospective study from adolescence to young adulthood. BMC Psychiatry. 2014;14:210. https://doi.org/10.1186/s12888-014-0210-2.

60. Weinstock LM, Whisman MA. Neuroticism as a common feature of the depressive and anxiety disorders: a test of the revised integrative hierarchical model in a national sample. J Abnorm Psychol. 2006;115(1):68–74. https://doi.org/10.1037/0021-843X.115.1.68.

61. Zinbarg RE, Mineka S, Bobova L, Craske MG, Vrshek-Schallhorn S, Griffith JW, Wolitzky-Taylor K, Waters AM, Sumner JA, Anand D. Testing a hierarchical model of neuroticism and its cognitive facets: latent structure and prospective prediction of first onsets of anxiety and unipolar mood disorders during 3 years in late adolescence. Clin Psychol Sci. 2016;4(5):805–24. https://doi.org/10.1177/2167702615618162.

62. Reiss S, McNally RJ. Expectancy model of fear. In: Reiss S, Bootzin R, editors. Theoretical issues in behavior therapy. San Diego: Academic; 1985. p. 107–21.

63. Rector NA, Szacun-Shimizu K, Leybman M. Anxiety sensitivity within the anxiety disorders: disorder-specific sensitivities and depression comorbidity. Behav Res Ther. 2007;45(8):1967–75. https://doi.org/10.1016/j.brat.2006.09.017.

64. Allan NP, Capron DW, Raines AM, Schmidt NB. Unique relations among anxiety sensitivity factors and anxiety, depression, and suicidal ideation. J Anxiety Disord. 2014a;28(2):266–75. https://doi.org/10.1016/j.janxdis.2013.12.004.

65. Allan NP, Macatee RJ, Norr AM, Schmidt NB. Direct and interactive effects of distress tolerance and anxiety sensitivity on generalized anxiety and depression. Cogn Ther Res. 2014b;38(5):530–40. https://doi.org/10.1007/s10608-014-9623-y.

66. Johnson SL, Turner RJ, Iwata N. BIS/BAS levels and psychiatric disorder: an epidemiological study. J Psychopathol Behav Assess. 2003;25(1):25–36. https://doi.org/10.1023/A:1022247919288.

67. Nigg JT. Temperament and developmental psychopathology. J Child Psychol Psychiatry. 2006;47(3–4):395–422. https://doi.org/10.1111/j.1469-7610.2006.01612.x.

68. Chronis-Tuscano A, Degnan KA, Pine DS, Perez-Edgar K, Henderson HA, Diaz Y, Raggi VL, Fox NA. Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. J Am Acad Child Adolesc Psychiatry. 2009;48(9):928–35. https://doi.org/10.1097/CHI.0b013e3181ae09df.

69. Rosenbaum JF, Biederman J, Hirshfeld-Becker DR, Kagan J, Snidman N, Friedman D, Nineberg A, Gallery DJ, Faraone SV. A controlled study of behavioral inhibition in children of parents with panic disorder and depression. Am J Psychiatry. 2000;157(12):2002–10. https://doi.org/10.1176/appi.ajp.157.12.2002.

70. Gentes EL, Ruscio AM. A meta-analysis of the relation of intolerance of uncertainty to symptoms of generalized anxiety disorder, major depressive disorder, and obsessive-compulsive disorder. Clin Psychol Rev. 2011;31(6):923–33. https://doi.org/10.1016/j.cpr.2011.05.001.

71. Kotov R, Gamez W, Schmidt F, Watson D. Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychol Bull. 2010;136(5):768–821. https://doi.org/10.1037/a0020327.

72. Britton JC, Lissek S, Grillon C, Norcross MA, Pine DS. Development of anxiety: the role of threat appraisal and fear learning. Depress Anxiety. 2011;28(1):5–17. https://doi.org/10.1002/da.20733.

73. Bittner A, Goodwin RD, Wittchen H-U, Beesdo K, Höfler M, Lieb R. What characteristics of primary anxiety disorders predict subsequent major depressive disorder? J Clin Psychiatry. 2004;65(5):618–26, quiz 730.

74. Garber J, Weersing VR. Comorbidity of anxiety and depression in youth: implications for treatment and prevention. Clin Psychol. 2010;17(4):293–306. https://doi.org/10.1111/j.1468-2850.2010.01221.x.

75. Starr LR, Davila J. Responding to anxiety with rumination and hopelessness: mechanism of anxiety-depression symptom co-occurrence? Cogn Ther Res. 2012;36(4):321–37. https://doi.org/10.1007/s10608-011-9363-1.

76. Conklin LR, Cassiello-Robbins C, Brake CA, Sauer-Zavala S, Farchione TJ, Ciraulo DA, Barlow DH. Relationships among adaptive and maladaptive emotion regulation strategies and psychopathology during the treatment of comorbid anxiety and alcohol use disorders. Behav Res Ther. 2015;73:124–30. https://doi.org/10.1016/j.brat.2015.08.001.

77. Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies revisited: a systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. Inflamm Bowel Dis. 2016;22(3):752–62. https://doi.org/10.1097/MIB.0000000000000620.

78. Baldwin DS. Serotonin noradrenaline reuptake inhibitors: a new generation of treatment for anxiety disorders. Int J Psychiatry Clin Pract. 2006;10(Suppl 2):12–5. https://doi.org/10.1080/13651500600637056.

79. Simon NM, Rosenbaum JF. Anxiety and depression comorbidity: implications and intervention. 2003. Retrieved from http://www.medscape.com/viewarticle/451325_print

80. Wuthrich VM, Rapee RM. Randomised controlled trial of group cognitive behavioural therapy for comorbid anxiety and depression in older adults. Behav Res Ther. 2013;51(12):779–86. https://doi.org/10.1016/j.brat.2013.09.002.

81. Barlow DH, Allen LB, Choate ML. Toward a unified treatment for emotional disorders. Behav Ther. 2004;35(2):205–30. https://doi.org/10.1016/S0005-7894(04)80036-4.

82. Barlow DH, Farchione TJ, Bullis JR, Gallagher MW, Murray-Latin H, Sauer-Zavala S, Bentley KH, Thompson-Hollands J, Conklin LR, Boswell JF, Ametaj A, Carl JR, Boettcher HT, Cassiello-Robbins C. The unified protocol for transdiagnostic treatment of emotional disorders compared with diagnosis-specific protocols for anxiety disorders: a randomized clinical trial. JAMA Psychiat. 2017;74(9):875–84. https://doi.org/10.1001/jamapsychiatry.2017.2164.

83. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits: a meta-analysis. J Psychosom Res. 2004;57(1):35–43. https://doi.org/10.1016/S0022-3999(03)00573-7.

84. A-Tjak JGL, Davis ML, Morina N, Powers MB, Smits JAJ, Emmelkamp PMG. A meta-analysis of the efficacy of acceptance and commitment therapy for clinically relevant mental and physical health problems. Psychother Psychosom. 2015;84(1):30–6. https://doi.org/10.1159/000365764.

85. Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, Brutsché NE, Ameli R, Furey ML, Zarate CA. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res. 2014;58:161–6. https://doi.org/10.1016/j.jpsychires.2014.07.027.

86. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, Axmacher N, Lemke M, Cooper-Mahkorn D, Cohen MX, Brockmann H, Lenartz D, Sturm V, Schlaepfer TE. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry. 2010;67(2):110–6. https://doi.org/10.1016/j. biopsych.2009.09.013.

87. Schiffer F, Johnston AL, Ravichandran C, Polcari A, Teicher MH, Webb RH, Hamblin MR. Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety. Behav Brain Funct. 2009;5(1):46. https://doi.org/10.1186/1744-9081-5-46.

88. Amir N, Beard C, Cobb M, Bomyea J. Attention modification program in individuals with generalized anxiety disorder. J Abnorm Psychol. 2009;118(1):28–33. https://doi.org/10.1037/a0012589.

89. Hakamata Y, Lissek S, Bar-Haim Y, Britton JC, Fox N, Leibenluft E, Ernst M, Pine DS. Attention Bias modification treatment: a meta-analysis towards the establishment of novel treatment for anxiety. Biol Psychiatry. 2010;68(11):982–90. https://doi.org/10.1016/j. biopsych.2010.07.021.

90. Rapee RM, MacLeod C, Carpenter L, Gaston JE, Frei J, Peters L, Baillie AJ. Integrating cognitive bias modification into a standard cognitive behavioural treatment package for social phobia: a randomized controlled trial. Behav Res Ther. 2013;51(4):207–15. https://doi.org/10.1016/j.brat.2013.01.005.

91. Lazarov A, Suarez-Jimenez B, Tamman A, Falzon L, Zhu X, Edmondson DE, Neria Y. Attention to threat in posttraumatic stress disorder as indexed by eye-tracking indices: a systematic review. Psychol Med. 2018:1–22. https://doi.org/10.1017/S0033291718002313.

92. Hardin MG, Schroth E, Pine DS, Ernst M. Incentive-related modulation of cognitive control in healthy, anxious, and depressed adolescents: development and psychopathology related differences. J Child Psychol Psychiatry. 2007;48(5):446–54. https://doi.org/10.1111/j.1469-7610.2006.01722.x.

93. Siegle GJ, Ghinassi F, Thase ME. Neurobehavioral therapies in the 21st century: summary of an emerging field and an extended example of cognitive control training for depression. Cogn Ther Res. 2007;31(2):235–62. https://doi.org/10.1007/s10608-006-9118-6.

94. Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, et al. Developing constructs for psychopathology research: research domain criteria. J Abnorm Psychol. 2010;119(4):631.

95. Watson D. Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. J Abnorm Psychol. 2005;114(4):522.

96. Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. Am J Psychiatr. 2014;171(4):395–7.

97. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013;11(1):126.

98. Calkins AW, McMorran KE, Siegle GJ, Otto MW. The effects of computerized cognitive control training on community adults with depressed mood. Behav Cogn Psychother. 2015;43(5):578–89.

99. Merikangas KR, Mehta RL, Molnar BE, Walters EE, Swendsen JD, Aguilar-Gaziola S, Bijl R, Borges G, Caraveo-Anduaga JJ, DJ DW, Kolody B, Vega WA, Wittchen HU, Kessler RC. Comorbidity of substance use disorders with mood and anxiety disorders: results of the international consortium in psychiatric epidemiology. Addict Behav. 1998;23(6):893–907. https://doi.org/10.1016/S0306-4603(98)00076-8.

100. Robinson J, Sareen J, Cox BJ, Bolton JM. Role of self-medication in the development of comorbid anxiety and substance use disorders: a longitudinal investigation. Arch Gen Psychiatry. 2011;68(8):800–7. https://doi.org/10.1001/archgenpsychiatry.2011.75.

101. de Graaf R, Bijl RV, ten Have M, Beekman ATF, Vollebergh WAM. Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. J Affect Disord. 2004;82(3):461–7. https://doi.org/10.1016/j.jad.2004.03.001.

102. de Graaf R, Bijl RV, Spijker J, Beekman ATF, Vollebergh WAM. Temporal sequencing of lifetime mood disorders in relation to comorbid anxiety and substance use disorders. Soc Psychiatry Psychiatr Epidemiol. 2003;38(1):1–11. https://doi.org/10.1007/s00127-003-0597-4.

103. Howland RH, John Rush A, Wisniewski SR, Trivedi MH, Warden D, Fava M, Davis LL, Balasubramani GK, PJ MG, Berman SR. Concurrent anxiety and substance use disorders among outpatients with major depression: clinical features and effect on treatment outcome. Drug Alcohol Depend. 2009;99(1):248–60. https://doi.org/10.1016/j.drugalcdep.2008.08.010.

104. Buckner JD, Heimberg RG, Ecker AH, Vinci C. A biopsychosocial model of social anxiety and substance use. Depress Anxiety. 2013;30(3):276–84. https://doi.org/10.1002/da.22032.

105. Cox BJ, Ron Norton G, Swinson RP, Endler NS. Substance abuse and panic-related anxiety: a critical review. Behav Res Ther. 1990;28(5):385–93. https://doi.org/10.1016/0005-7967(90)90157-E.

106. Magidson JF, Liu S-M, Lejuez CW, Blanco C. Comparison of the course of substance use disorders among individuals with and without generalized anxiety disorder in a nationally representative sample. J Psychiatr Res. 2012;46(5):659–66. https://doi.org/10.1016/j.jpsychires.2012.02.011.

107. McHugh RK. Treatment of co-occurring anxiety disorders and substance use disorders. Harv Rev Psychiatry. 2015;23(2):99–111. https://doi.org/10.1097/HRP.0000000000000058.

108. Bruce SE, Yonkers KA, Otto MW, Eisen JL, Weisberg RB, Pagano M, Shea MT, Keller MB. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry. 2005;162(6):1179–87. https://doi.org/10.1176/appi.ajp.162.6.1179.

109. Boschloo L, Vogelzangs N, van den Brink W, Smit JH, Veltman DJ, Beekman ATF, Penninx BWJH. Alcohol use disorders and the course of depressive and anxiety disorders. Br J Psychiatry J Ment Sci. 2012;200(6):476–84. https://doi.org/10.1192/bjp.bp.111.097550.

110. Cooper ML, Frone MR, Russell M, Mudar P. Drinking to regulate positive and negative emotions: a motivational model of alcohol use. J Pers Soc Psychol. 1995;69(5):990–1005.

111. Wolitzky-Taylor K, Bobova L, Zinbarg RE, Mineka S, Craske MG. Longitudinal investigation of the impact of anxiety and mood disorders in adolescence on subsequent substance use disorder onset and vice versa. Addict Behav. 2012;37(8):982–5. https://doi.org/10.1016/j.addbeh.2012.03.026.

112. de Graaf R, Bijl RV, Smit F, Vollebergh WAM, Spijker J. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands mental health survey and incidence study. Am J Psychiatry. 2002;159(4):620–9. https://doi.org/10.1176/appi.ajp.159.4.620.

113. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry. 2003;60(9):929–37. https://doi.org/10.1001/archpsyc.60.9.929.

114. Compton WM 3rd, Cottler LB, Ben Abdallah A, Phelps DL, Spitznagel EL, Horton JC. Substance dependence and other psychiatric disorders among drug dependent subjects: race and gender correlates. Am J Addict. 2000;9(2):113–25.

115. Kendler KS, Davis CG, Kessler RC. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. Br J Psychiatry. 1997;170(6):541–8. https://doi.org/10.1192/bjp.170.6.541.

116. Nicholls J, Staiger PK, Williams JS, Richardson B, Kambouropoulos N. When social anxiety co-occurs with substance use: does an impulsive social anxiety subtype explain this unexpected relationship? Psychiatry Res. 2014;220(3):909–14. https://doi.org/10.1016/j.psychres.2014.08.040.

117. Jakuszkowiak-Wojten K, Landowski J, Wiglusz MS, Cubała WJ. Impulsivity in anxiety disorders. A critical review. Psychiatr Danub. 2015;27(Suppl 1):S452–5.

118. Perry JL, Carroll ME. The role of impulsive behavior in drug abuse. Psychopharmacology. 2008;200(1):1–26. https://doi.org/10.1007/s00213-008-1173-0.
119. Bevilacqua L, Goldman D. Genetics of impulsive behaviour. Philos Trans R Soc B. 2013;368(1615). https://doi.org/10.1098/rstb.2012.0380.
120. Anokhin AP, Grant JD, Mulligan RC, Heath AC. The genetics of impulsivity: evidence for the heritability of delay discounting. Biol Psychiatry. 2015;77(10):887–94. https://doi.org/10.1016/j.biopsych.2014.10.022.
121. Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, Prescott CA. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and Cotwin control analysis. Arch Gen Psychiatry. 2000a;57(10):953–9. https://doi.org/10.1001/archpsyc.57.10.953.
122. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Childhood parental loss and adult psychopathology in women: a twin study perspective. Arch Gen Psychiatry. 1992a;49(2):109–16. https://doi.org/10.1001/archpsyc.1992.01820020029004.
123. Kendler KS, Myers J, Prescott CA. Parenting and adult mood, anxiety and substance use disorders in female twins: an epidemiological, multi-informant, retrospective study. Psychol Med. 2000b;30(2):281–94.
124. Cattell RB. The meaning and measurement of neuroticism and anxiety: supplement to a review. Br J Soc Clin Psychol. 1963;2(3):224–6. https://doi.org/10.1111/j.2044-8260.1963.tb00394.x.
125. Brown RA, Kahler CW, Zvolensky MJ, Lejuez CW, Ramsey SE. Anxiety sensitivity: relationship to negative affect smoking and smoking cessation in smokers with past major depressive disorder. Addict Behav. 2001;26(6):887–99. https://doi.org/10.1016/S0306-4603(01)00241-6.
126. Leventhal AM, Zvolensky MJ. Anxiety, depression, and cigarette smoking: a transdiagnostic vulnerability framework to understanding emotion-smoking comorbidity. Psychol Bull. 2015;141(1):176–212. https://doi.org/10.1037/bul0000003.
127. Zvolensky MJ, Marshall EC, Johnson K, Hogan J, Bernstein A, Bonn-Miller MO. Relations between anxiety sensitivity, distress tolerance, and fear reactivity to bodily sensations to coping and conformity marijuana use motives among young adult marijuana users. Exp Clin Psychopharmacol. 2009;17(1):31–42. https://doi.org/10.1037/a0014961.
128. Simons JS, Gaher RM. The distress tolerance scale: development and validation of a self-report measure. Motiv Emot. 2005;29(2):83–102. https://doi.org/10.1007/s11031-005-7955-3.
129. Leyro TM, Zvolensky MJ, Bernstein A. Distress tolerance and psychopathological symptoms and disorders: a review of the empirical literature among adults. Psychol Bull. 2010;136(4):576–600. https://doi.org/10.1037/a0019712.
130. Daughters SB, Reynolds EK, MacPherson L, Kahler CW, Danielson CK, Zvolensky M, Lejuez CW. Distress tolerance and early adolescent externalizing and internalizing symptoms: the moderating role of gender and ethnicity. Behav Res Ther. 2009;47(3):198–205. https://doi.org/10.1016/j.brat.2008.12.001.
131. Watkins KE, Hunter SB, Burnam MA, Pincus HA, Nicholson G. Review of treatment recommendations for persons with a co-occurring affective or anxiety and substance use disorder. Psychiatr Serv. 2005;56(8):913–26. https://doi.org/10.1176/appi.ps.56.8.913.
132. Brady KT, Verduin ML. Pharmacotherapy of comorbid mood, anxiety, and substance use disorders. Subst Use Misuse. 2005;40(13–14):2021–41. https://doi.org/10.1080/10826080500294924.
133. Danion JM, Neunreuther C, Krieger-Finance F, Imbs JL, Singer L. Compliance with long-term lithium treatment in major affective disorders. Pharmacopsychiatry. 1987;20(5):230–1. https://doi.org/10.1055/s-2007-1017111.
134. Schadé A, Marquenie LA, van Balkom AJLM, Koeter MWJ, de Beurs E, van Dyck R, van den Brink W. Anxiety disorders: treatable regardless of the severity of comorbid alcohol dependence. Eur Addict Res. 2007;13(2):109–15. https://doi.org/10.1159/000097941.

135. Kushner MG, Maurer EW, Thuras P, Donahue C, Frye B, Menary KR, Hobbs J, Haeny AM, Van Demark J. Hybrid cognitive behavioral therapy versus relaxation training for co-occurring anxiety and alcohol disorder: a randomized clinical trial. J Consult Clin Psychol. 2013;81(3):429–42. https://doi.org/10.1037/a0031301.

136. Roy-Byrne PP, Davidson KW, Kessler RC, Asmundson GJG, Goodwin RD, Kubzansky L, Lydiard RB, Massie MJ, Katon W, Laden SK, Stein MB. Anxiety disorders and comorbid medical illness. Gen Hosp Psychiatry. 2008;30(3):208–25. https://doi.org/10.1016/j.genhosppsych.2007.12.006.

137. Sareen J, Cox BJ, Stein MB, Afifi TO, Fleet C, Asmundson GJG. Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. Psychosom Med. 2007;69(3):242–8. https://doi.org/10.1097/PSY.0b013e31803146d8.

138. Asmundson GJG, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. Depress Anxiety. 2009;26(10):888–901. https://doi.org/10.1002/da.20600.

139. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J Pain. 2015;16(8):769–80. https://doi.org/10.1016/j.jpain.2015.05.002.

140. Fishbain DA, Goldberg M, Meagher BR, Steele R, Rosomoff H. Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria. Pain. 1986;26(2):181–97.

141. Large RG. DSM-III diagnoses in chronic pain. Confusion or clarity? J Nerv Ment Dis. 1986;174(5):295–303.

142. Reich J, Tupin JP, Abramowitz SI. Psychiatric diagnosis of chronic pain patients. Am J Psychiatry. 1983;140(11):1495–8. https://doi.org/10.1176/ajp.140.11.1495.

143. Atkinson JH, Slater MA, Patterson TL, Grant I, Garfin SR. Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: a controlled study. Pain. 1991;45(2):111–21.

144. Kinney RK, Gatchel RJ, Polatin PB, Fogarty WT, Mayer TG. Prevalence of psychopathology in acute and chronic low back pain patients. J Occup Rehabil. 1993;3(2):95–103. https://doi.org/10.1007/BF01078162.

145. Polatin PB, Kinney RK, Gatchel RJ, Lillo E, Mayer TG. Psychiatric illness and chronic low-back pain. The mind and the spine – which goes first? Spine. 1993;18(1):66–71.

146. Asmundson GJG, Taylor S. Role of anxiety sensitivity in pain-related fear and avoidance. J Behav Med. 1996;19(6):577–86. https://doi.org/10.1007/BF01904905.

147. Krishnan KRR, France RD, Pelton S, McCann UD, Davidson J, Urban BJ. Chronic pain and depression. II. Symptoms of anxiety in chronic low back pain patients and their relationship to subtypes of depression. Pain. 1985;22(3):289–94. https://doi.org/10.1016/0304-3959(85)90029-6.

148. Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosom Med. 2008;70(8):890–7. https://doi.org/10.1097/PSY.0b013e318185c510.

149. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain. 2003;106(1):127–33. https://doi.org/10.1016/S0304-3959(03)00301-4.

150. McCracken LM, Gross RT. Does anxiety affect coping with chronic pain? Clin J Pain. 1993;9(4):253–9.

151. Teh CF, Morone NE, Karp JE, Belnap BH, Zhu F, Weiner DK, Rollman BL. Pain interference impacts response to treatment for anxiety disorders. Depress Anxiety. 2009;26(3):222–8. https://doi.org/10.1002/da.20514.

152. McCracken LM, Dhingra L. A short version of the pain anxiety symptoms scale (PASS-20): preliminary development and validity. Pain Res Manag. 2002;7(1):45–50.

153. Rogers AH, Bakhshaie J, Lam H, Langdon KJ, Ditre JW, Zvolensky MJ. Pain-related anxiety and opioid misuse in a racially/ethnically diverse young adult sample with moderate/severe pain. Cogn Behav Ther. 2018:1–11. https://doi.org/10.1080/16506073.2018.1436085.

154. LaRowe LR, Langdon KJ, Zvolensky MJ, Zale EL, Ditre JW. Pain-related anxiety as a predictor of early lapse and relapse to cigarette smoking. Exp Clin Psychopharmacol. 2017;25(4):255–64. https://doi.org/10.1037/pha0000127.
155. Kindt M, Soeter M, Vervliet B. Beyond extinction: erasing human fear responses and preventing the return of fear. Nat Neurosci. 2009;12(3):256–8. https://doi.org/10.1038/nn.2271.
156. Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, Stacey B, Tepper S. Efficacy of gabapentin in migraine prophylaxis. Headache. 2001;41(2):119–28.
157. Urquhart DM, Hoving JL, Assendelft WWJJ, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. Cochrane Database Syst Rev. 2008;(1):CD001703. https://doi.org/10.1002/14651858.CD001703.pub3.
158. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain. 1999;80(1):1–13. https://doi.org/10.1016/S0304-3959(98)00255-3.
159. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2012;11:CD007407. https://doi.org/10.1002/14651858.CD007407.pub3.
160. Veehof MM, Oskam M-J, Schreurs KMG, Bohlmeijer ET. Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. Pain. 2011;152(3):533–42. https://doi.org/10.1016/j.pain.2010.11.002.
161. Wetherell JL, Afari N, Rutledge T, Sorrell JT, Stoddard JA, Petkus AJ, Solomon BC, Lehman DH, Liu L, Lang AJ, Hampton Atkinson J. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. Pain. 2011;152(9):2098–107. https://doi.org/10.1016/j.pain.2011.05.016.
162. Vlaeyen JW, de Jong J, Sieben J, Crombez G. Graded exposure in vivo for pain-related fear. In: Turk DC, Gatchel RJ, editors. Psychological approaches to pain management: a practioner's handbook. 2nd ed. New York: Guilford Press; 2002. p. 210–33.

Chapter 6
From OC Spectrum to Anxiety Disorders

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Obsessive-compulsive and related disorders (OCRDs) consist of a cluster of impairing psychological conditions including obsessive-compulsive disorder (OCD), body dysmorphic disorder (BDD), hoarding disorder, hair-pulling disorder (i.e., trichotillomania), skin-picking disorder (i.e., excoriation), and other specified and unspecified OCRDs [1]. Broadly, these conditions present with some overlap in symptomatology, theorized mechanisms, and evidence-based treatment approaches. However, there is significant heterogeneity across OCRDs and notable nuances in conceptualizing individual disorders within this class [2]. Moreover, there is significant heterogeneity in the presentation of symptoms within diagnoses, such as OCD, with symptoms varying considerably both between and within clients over time [3, 4]. Complicating this picture further, OCRDs often co-occur with anxiety disorders, and in some cases, symptoms share considerable overlap in appearance or function [5, 6]. Indeed, OCD was considered an anxiety disorder until the most recent revision of the Diagnostic and Statistical Manual of Mental Disorders in 2013 (DSM-5; [1]). As such, a fine-grained understanding of each anxiety and OC spectrum condition, and a functional analysis of symptoms, is necessary to facilitate accurate diagnosis, case conceptualization, and optimal treatment planning for OC and anxiety disorders.

In the present chapter, we will first provide an overview of the current diagnostic criteria for OCRDs. We will briefly highlight critiques and important considerations concerning the conceptualization of OCRDs in the DSM-5. We will review

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the cognitive-behavioral model of OCRDs, highlighting conceptual overlap with anxiety disorders as well as clinically important nuances. We will provide practical, evidence-based recommendations for functional assessment and case conceptualization and highlight considerations for differential diagnosis among OCRDs and anxiety disorders. Lastly, we will discuss empirically supported interventions and relevant treatment considerations, particularly concerning comorbidity and diagnostic-specific versus transdiagnostic interventions.

DSM-5 and Clinical Features: The Obsessive-Compulsive and Related Disorders (OCRDs)

With the publication of the DSM-5, the organization of anxiety disorders and OCRDs was significantly revised [1]. Specifically, the creation of the OCRDs class in DSM-5 involved the following reclassifications and changes: OCD was moved from the anxiety disorders, BDD from the somatoform disorders, and hair-pulling disorder (previously trichotillomania) from the impulse control disorders; hoarding was distinguished as a separate diagnosis, rather than a symptom of OCD; and excoriation (skin-picking) disorder was added as a new diagnosis, not previously included in the DSM.

As noted, OCD was previously classified as an anxiety disorder (alongside specific phobias, panic disorder, social anxiety disorder, and generalized anxiety disorder) due to the considerable overlap between their conceptual models and empirically supported treatments. Generally, anxiety disorders and OCD both involve chronic, impairing affective states of fear, anxiety, and distress and functionally related behaviors, including avoidance of feared stimuli and safety behaviors aimed to reduce perceived threat and distress. However, some research suggests that OCD might be better conceptualized along a spectrum of related conditions that are characterized by the repeated, compulsive nature of behavioral symptoms rather than cognitive-affective symptoms [7, 8]. Thus, this reconceptualization switched the unifying emphasis from a functional model centered around affectively motivated avoidance and impairment to one focused on observable, recurrent behavioral symptoms. Such repetitive actions were hypothesized to more precisely indicate shared neurobiological diatheses, and thus this new categorization was suggested to have greater utility to clinical practice (e.g., indicating optimal treatments) as well as research aimed to advance our understanding of the causal mechanisms of OCRDs.

Broadly, the OCRDs are characterized by compulsive cognitive and/or behavioral phenomena. However, the function of these behaviors may differ considerably across OCRDs and include symptoms that involve anxiety or distress or yield gratification and positive reinforcement. This discrepancy is best evidenced in considerable research highlighting the functional overlap between the phenomenology of several OCRDs (e.g., skin-picking and hair-pulling disorder) and addictive spectrum concerns [9, 10]. As can be noted in reviewing the ORCD class in the sections that

follow, several conditions share greater conceptual and treatment overlap with shared cognitive-behavioral mechanistic and maintenance processes (e.g., anxiety disorders, OCD, BDD), while other OCRDs present more specialized considerations and distinctive conceptual models and treatments (e.g., hair-pulling, skin-picking, hoarding disorder).

Diagnostic Criteria

First, a few common diagnostic criteria present transdiagnostically across OCRDs in the DSM-5 [1]. The central symptoms of each disorder must be causing substantial distress or impairment across multiple meaningful domains of functioning (e.g., socially, at work or school, in one's ability to perform daily activities). Research has supported that many OCRD symptoms are highly prevalent and occur on a spectrum of severity within the population (e.g., intrusive thoughts, body image concerns, hair pulling, skin picking) [e.g., 11–14]. This impairment criterion is thus particularly important in distinguishing clinical phenomena that warrant intervention. Additionally, OCRD symptoms must not be the result of a diagnosed medical condition (e.g., neurological disorder, dermatological condition, specific disease) or the result of substance use behavior (e.g., cocaine). Similarly, primary symptoms must not be more robustly explained by or attributed to another psychological condition. This last distinction can be particularly challenging in terms of differential diagnosis within the OC spectrum or between OCRDs, anxiety disorders, and other conditions (e.g., psychosis, eating disorders). As such, considerations and tools are provided below (see Differential Diagnoses) for anxiety-related conditions that are commonly misdiagnosed or co-occur with OCRDs.

Obsessive-Compulsive Disorder (OCD)

OCD is characterized by the presence of either obsessions or compulsions that cause significant distress and impairment across several domains of functioning (e.g., occupational, interpersonal) [1]. *Obsessions* are defined as recurring thoughts, urges, or images, which lead to anxiety or distress (e.g., the fear that one has been contaminated by germs, an image of hitting a pedestrian while driving). If it is not possible to avoid obsessional thoughts, individuals with OCD attempt to eliminate, reduce, neutralize, or suppress these intrusive cognitions, either with another thought (e.g., a prayer to keep a loved one safe) or action (e.g., handwashing). *Compulsions* are repetitive mental or physical actions that the individual engages in following an obsession or in adherence to specific rules. These behaviors are performed in order to alleviate distress (e.g., anxiety) or to prevent feared outcomes (e.g., checking the locks repeatedly to prevent a break-in). As such, compulsions are time-consuming, impairing behaviors that are either not directly connected with feared outcomes (e.g., compulsive counting to prevent a disaster from impacting

one's family) or are excessive in response to actual threat (e.g., washing hands for 30 minutes after cooking with raw meat). Further, compulsions may be *overt* or *covert*, involving either observable behaviors (e.g., reassurance seeking, cleaning, ordering) or internalized mental acts (e.g., counting, praying, reviewing one's actions to assure that something was done properly). In this way, despite the DSM-5 criteria that requires only obsessions *or* compulsions be present to meet criteria for OCD, research indicates that 96% of individuals with OCD report both obsessions *and* compulsions [15]. For this reason, it is particularly important to comprehensively assess for covert rituals if a client presents with significant obsessions without overt compulsions.

Insight Criterion An insight criterion is also included for OCD in DSM-5. This specifier identifies the individual as possessing (1) good or fair, (2) poor, or (3) absent insight. In the case of *good or fair* insight, a client will identify that obsessive beliefs and intrusive thoughts are definitively or likely not true (e.g., viewing them as unreasonable or senseless; e.g., a woman with distressing intrusive thoughts about accidentally poisoning her children with chemicals may believe that it is unlikely that using more detergent than recommended will harm her children, but she thinks it is "better to be safe than sorry"). For an individual with *poor* insight, obsessive beliefs and intrusive thoughts are reported to likely be true; however, these individuals are able to recognize that there is a chance that these beliefs are inaccurate. Lastly, a client with absent insight will present with a solid conviction that obsessions and beliefs are true and accurate (e.g., "I had this thought because I certainly made a mistake that will poison my children"). In these cases, intrusive thoughts may present as delusional beliefs, and individuals may appear out of touch with reality. Of note, poor insight in OCD is fairly uncommon and absent or delusional insight even less so [16].

Subtypes and Symptom Dimensions As mentioned, the presentation of obsessions and compulsions in OCD is highly idiosyncratic and can shift over time. Although subtypes of OCD are not formally included in the DSM-5, research suggests that obsessions tend to cohere along four primary themes including (1) fears of germs, contamination, and illness, (2) responsibility for causing harm or making a mistake, (3) thoughts about unacceptable or taboo topics (i.e., sexual, violent, immoral, or blasphemous themes), or (4) a need for symmetry, order, and exactness [4, 17]. Within these four dimensions, obsessions and compulsions are coupled together in thematic content. For example, an intrusive thought regarding contamination (e.g., "The toilet in the public restroom is covered with germs that will spread HIV/AIDs") is typically linked with a compulsion aimed to prevent getting sick and reduce resulting anxiety (e.g., washing one's hands for 15 minutes to eliminate the perceived contaminant). However, obsessions and compulsions can couple across symptom dimensions; for instance, an individual may wash his hands to rid himself of sin following an unwanted blasphemous thought. This unique heterogeneity in OCD underscores the need for careful, comprehensive assessment as further described below (see Considerations for Assessment and Diagnosis).

Prevalence and Course   OCD is estimated to impact 1–2% of the US population in a given year, with parallel estimates internationally [18, 19]. Symptoms typically onset around age 20, with the first onset of symptoms possible but rare in pediatric populations or in individuals over the age of 35 [19–21]. The prevalence rates of OCD are similar across men and women; however, symptoms typically onset earlier in men (resulting in more boys with OCD compared to girls) [22]. In general, symptoms onset gradually; yet, in certain circumstances (e.g., perinatal OCD), a rapid onset of severe symptoms can occur [23]. The severity of symptoms tends to oscillate over time, with a long-term trend toward worsening severity and impairment without treatment [24]. Despite several highly effective, empirically supported treatments (e.g., exposure therapy), the majority of individuals with OCD do not receive treatment, and clients suffer for on average 10–17 years prior to receiving care [25]. Moreover, full remission rates in the community remain quite low [20, 26]. Collectively, these factors highlight the considerable impairment, disability, and distress associated with OCD.

Body Dysmorphic Disorder (BDD)

In terms of diagnostic criteria and presentation, BDD mostly closely aligns with OCD within the OCRD spectrum. In order to meet criteria for BDD, an individual must report marked concerns with at least one perceived fault or problem with their physical appearance [1]. This reported physical defect must either be unobservable to others or deemed excessive and disproportionate to the flaw. In response to this appearance-centered distress, individuals with BDD engage in repetitive physical (e.g., mirror checking, reassurance seeking) and/or mental (e.g., comparing his or her appearance with that of others) behaviors. Additionally, individuals with BDD engage in patterns of avoidance (e.g., of having their photograph taken, leaving the house to interact with others) aimed to prevent or reduce distress. As noted for OCD, these intrusive cognitions, rituals, and avoidance cause substantial distress as well as impairment in various domains of functioning (e.g., social interactions, workplace performance).

Muscle Dysmorphia   In DSM-5, a specifier was included to identify individuals specifically preoccupied with weight and shape concerns centered on muscularity (a subtype that otherwise can be overlooked or mistaken for an eating disorder). This symptom presentation is far more common in men but can also present in women [27, 28].

Insight Criterion   As in OCD, an insight criterion (with the same three categories) is included in the DSM-5 definition of BDD. Clients with BDD are more likely than those with OCD to report poor or absent insight [16], endorsing statements with conviction such as "My nose looks dreadful and is severely deformed." Thus, low insight in the treatment of BDD can present a challenge (as discussed further in the Treatment Implications section below).

Prevalence and Course   BDD is estimated to affect 2% of the population, with higher rates observed among clients seeking medical or surgical treatment that impacts physical appearance (i.e., cosmetic surgery, dermatology) [29, 30]. In most cases, BDD onsets during adolescence (e.g., 12–17 years old) and progresses gradually over time [31]. However, the discrete trigger endorsed for BDD onset is often either unidentifiable or related to more diffuse, interpersonal events that contribute to a sensitized awareness of one's appearance, such as bullying or teasing [32]. Although BDD presents across the lifespan, its presentation among geriatric populations is lacking. Extant research supports that the prevalence and clinical characteristics of BDD are overall similar across men and women; however, men and women tend to differ in their body area of primary concern [27, 33]. Specifically, women are more likely to be preoccupied with their breasts/chest, skin, buttocks, thighs/legs, hips, toes, and excessive body/facial hair, while men are more likely to focus on body build, genitals, and hair thinning/balding.

Hoarding Disorder

To meet criteria for hoarding disorder, an individual must experience considerable difficulty with the disposal of possessions [1]. This difficulty arises from a strongly held desire to save items, and attempts to discard possessions elicit considerable distress (e.g., anxiety, anger). This distress is typically present for the majority of possessions and is the not the result of the specific monetary or sentimental value attached to a single item. In fact, individuals may acquire possessions without functional, monetary, or sentimental value (e.g., broken appliances, used food containers), due to a diverse number of reasons for saving [34]. The inability to discard possessions results in substantial clutter and impairment in daily activities. If the removal of items does occur, it usually is done by the intervention of others such as family members or authorities. Hoarding is considered of clinical significance if it is causing impairment in daily life activities and hindering functioning in interpersonal, workplace, or other meaningful domains. Of note, hoarding may uniquely result in impaired safety both for oneself and others (e.g., neighbors, children, pets) in the immediate living environment due to excessive clutter [35].

Excessive Acquisition Criterion   Within DSM-5, it is possible to specify whether an individual presents with excessive acquisition (i.e., excessive buying or collecting). It is more common for women to engage in compulsive buying of items, whereas the excessive acquisition of free items tends to be similar in men and women [36]. This criterion may indicate overall clinical severity, given the relationship between compulsive buying and hoarding symptom severity [37, 38].

Insight Criterion   The degree of insight (good or fair, poor, absent) in hoarding disorder can vary considerably between individuals. Although these three insight categories overlap with OCD and BDD, insight for hoarding disorder focuses on whether the individual recognizes the degree to which hoarding symptoms are caus-

ing problems and impairment. For example, an individual with poor or absent insight will hold a strong conviction that the excessive acquisition and inability to discard possessions are not a source of impairment.

Prevalence and Course In comparison with OCD, accurate prevalence estimates of hoarding disorder are lacking, with best estimates indicating that 2–6% of the US population is impacted by this condition [39]. Although symptoms typically begin in adolescence, similar to other OCRDs, individuals typically are diagnosed and present for treatment significantly later in life [40]. Further, individuals with hoarding symptoms are less to likely to present for treatment than other OCRDs (or they present for delayed treatment), given that treatment seeking is typically due to extrinsic motivations (e.g., encouragement to seek care by loved ones or due to legal ramifications) [41, 42]. This also contributes to the challenging nature of treating hoarding, as discussed in Treatment Implications below. Those with severe hoarding symptoms often struggle with additional impairments in interpersonal domains (e.g., conflict with family members, neighbors) as well as physical health consequences (e.g., due to the impact of clutter on sleep, movement, hygiene, etc.) [35].

Hair-Pulling Disorder (HPD)

To meet criteria for HPD, an individual must demonstrate repetitive, hair-pulling behavior that they are unable to control or stop, resulting in substantial hair loss [1]. The hair pulling must cause significant distress or impairment (e.g., social, personal, occupational, physical). Hair pulling must not solely occur as a means to improve physical appearance (e.g., cosmetic behavior) or correct a perceived blemish (e.g., as in BDD, to be discussed further in Differential Diagnosis) or as the result of another medical or psychological condition.

Prevalence and Course Recent estimates suggest that HPD impacts approximately 1–2% of the population [18, 19, 21]. The majority of individuals affected by HPD are women. It remains unclear the extent to which this gender discrepancy is inflated due to gender differences in cultural attitudes around hair loss and appearance or genetic/biological sex differences in the etiology of HPD. Hair pulling is fairly common in early developmental stages and typically extinguishes on its own [43, 44]. Moreover, as previously noted, it is not uncommon for individuals to engage in forms of hair removal (e.g., tweezing, physical pulling) for cosmetic purposes. When hair pulling persists and leads to significant physical consequences or distress, however, it is likely to result in a diagnosis of HPD. Although HPD typically onsets in adolescence, symptoms can onset at any age [45]. The severity of symptoms may oscillate over time, but typically do not fully remit without treatment [46]. Individuals with severe symptoms may experience significant physical health consequences (e.g., permanent hair follicle destruction) as a result of chronic hair pulling [47].

Skin-Picking (Excoriation) Disorder (SPD)

The criteria for SPD closely parallel those of HPD and are new to DSM-5 [1]. An individual with SPD experiences excessive, repeated skin picking that they are unable to control, reduce, or cease on their own. Importantly, the behavior causes considerable distress, physical health consequences (e.g., tissue damage, infection), or impairments in relationships, work, school, or other domains of functioning. Clients often present for treatment due to physical ramifications of picking, medical advice, or parental intervention.

Prevalence and Course SPD (i.e., excoriation, disorder) is estimated to impact 1–2% of the population, with community estimates suggesting a higher prevalence around 5% [12, 48]. As with HPD, rates are much higher among women than men. However, again the extent to which this represents a true biological versus cultural difference in prevalence remains unknown. Although SPD can onset at any age, symptoms often present earlier than other OCRDs in childhood or adolescence [49]. It is also common for skin picking to follow the onset of a dermatological condition, such as acne or a rash, and then to persist [50]. As with HPD, over time these behaviors become chronic and more severe, leading to impairment, and it is uncommon for symptoms to remit without treatment. Moreover, individuals may also experience significant health consequences (e.g., scarring, damaged tissue, infection) and necessitate medical intervention as a result of excoriation [51].

Case Conceptualization: Specificity and Overlap of Cognitive-Behavioral Models

Within anxiety disorders and OCRDs, there are a number of similarities across cognitive-behavioral formulations of central mechanisms and maintenance factors that contribute to the persistence and impairment of these conditions, particularly between anxiety disorders, OCD, and BDD. Given the context of this chapter and its emphasis on delineating OC spectrum conditions from anxiety, we first briefly review the cognitive-behavioral model of anxiety disorders before turning to the OCRDs. More extensive details and case examples across anxiety disorders can be found in Chap. 12.

Anxiety Disorders

Broadly, the cognitive-behavioral theory of anxiety disorders has been empirically validated through both applied research – on the cognitive-behavioral correlates, risk, and maintenance factors involved in anxiety disorders – and by the efficacy of cognitive-behavioral interventions for these conditions (see Chap. 12) [52, 53]. The

model is derived from Beck's [54] cognitive theory of psychopathology, which proposes that our appraisals and responses to internal experiences (i.e., cognitions, physiological sensations) cause the onset and maintenance of anxiety disorders. Specifically, clients with anxiety overestimate the likelihood as well as the severity of perceived threat (e.g., the likelihood of one's heart racing being a sign of a heart attack or the severity of a presentation at work going poorly) [55]. In this way, misappraisals or distorted patterns of thinking about specific situations and stimuli bring about excessive emotional responding (e.g., anxiety, worry, depression) as well as maladaptive avoidant or safety behaviors (e.g., taking one's pulse, over-preparing for the presentation) that are aimed to alleviate these distressing emotions or prevent a catastrophic, feared outcome (e.g., dying from a heart attack or losing one's job). While these behaviors may be effective in downregulating affective responding in the moment, they contribute to the exacerbation of symptoms over time by reinforcing inaccurate or unhelpful beliefs about perceived threat and preventing opportunities to naturalistically extinguish fear or correct such beliefs. This model manifests transdiagnostically across anxiety disorders; however, contextual and discrete triggers as well as the content of cognitions are diagnostic-specific, as will now be discussed for each OCRD. Moreover, key distinctions (e.g., for hoarding, SPD, HPD) will be outlined.

OCD

As with anxiety disorders, in the cognitive-behavioral model of OCD, core dysfunctional beliefs contribute to the development and maintenance of OCD symptoms [56, 57]. According to this model and empirical research [e.g., 13], unwanted, intrusive cognitions (e.g., thoughts, images, or urges involving contamination, symmetry, taboo topics, or harm) are highly prevalent phenomena (e.g., intrusive images of hitting someone with your car while driving). However, for individuals with OCD, these intrusions are misappraised as highly meaningful and significant (e.g., "Thinking about hitting someone with my car means that I am a dangerous person and likely to run someone over") rather than being dismissed as mental noise. When this occurs, the thought is likely to progress to a clinical obsession, as the misappraisal leads to significant fear, anxiety, and self-doubt. Furthermore, this motivates mental and behavioral actions to attempt to eliminate (e.g., thought suppression), reduce (e.g., checking the roads repeatedly to assure a pedestrian was not hit), or prevent (e.g., not driving at all) intrusions and resulting distress [e.g., 57]. As is observed for safety behaviors in anxiety disorders, compulsions are maintained via negative reinforcement (i.e., removing something aversive, in this case alleviating distress, such that the individual keeps performing these behaviors in the future). Compulsions also reinforce inaccurate overestimates of threat and beliefs about the meaning of and one's ability to tolerate internal experiences.

   This model can also be illustrated by a man with persistent, distressing intrusive thoughts about contracting HIV/AIDS while using a public restroom. In response to

the anxiety from these thoughts, he engages in extensive decontamination rituals (e.g., handwashing, showering) and seeks repeated reassurance from his partner and medical professionals to assure that he does not have HIV/AIDS. After engaging in these compulsions, he experiences immediate relief, reinforcing the behavior and increasing the likelihood that he will use them to regulate contamination fears in the future. However, he fails to learn that the negative outcome (e.g., developing HIV/AIDS) would likely not have occurred without his compulsions. Moreover, he is unable to learn that he can tolerate the distress of using public restrooms and his thoughts about contracting a serious medical condition. Thus, these compulsions continue to increase and begin to take a considerable interpersonal toll, leading to work impairment and relationship distress.

BDD

The cognitive-behavioral model of BDD involves similar functional relationships and mechanisms as those outlined for anxiety disorders and OCD [58, 59]. However, in BDD the dysfunctional beliefs and misappraisals involve a specific focus on perceived physical flaws and the significance of one's physical appearance. In this way, the functional relationships between BDD symptoms parallel that of anxiety disorders and OCD (e.g., the use of safety behaviors and avoidance to mitigate distress), while distinct symptoms also present that may warrant specific interventions (e.g., cognitions or behaviors more closely aligned with eating disorders, such as the overrevaluation of one's physical appearance). The triggers of symptoms tend to involve external perceptions of one's image (e.g., looking in a mirror, seeing a photograph) in which such physical flaws are overly attended to or exaggerated (e.g., the symmetry of one's facial features [60]), leading to a poor self-concept and distorted self-image. Attention is increasingly biased toward appearance concerns, which leads to a distorted cognitive schema of how the individual appears to others.

For example, an individual may experience preoccupation with the appearance of her nose (e.g., "My nose is enormous and hideous"). As a result, she compares her nose to that of celebrities, which further elicits feelings of disgust, hopelessness, and frustration with her physical appearance. This preoccupation contributes to overevaluation of appearance in her personal identity and leads her to anticipate rejection and judgment in social situations (e.g., "other people will feel disgusted and won't want to look at me"). In response to these unpleasant and distressing emotions, she engages in repeated behaviors to distract from her nose (e.g., long makeup routines to make her eyes more noticeable), to alleviate her distress about how noticeable her nose is to others (e.g., seeking reassurance from her partner and friends). She also avoids social situations in which she might encounter new people due to fear of embarrassment and rejection. As with OCD and anxiety, these behaviors effectively reduce her distress in the moment, but in the long-term, they serve to maintain the attentional bias toward her perceived defective nose, her feelings of inadequacy, and distorted thoughts around her image and the significance of her appearance.

Hoarding, Hair-Pulling Disorder, and Skin-Picking Disorder

Although there are some overlaps and similarities, hoarding, hair-pulling disorder, and skin-picking disorder are best explained through conceptual models distinct from those described for anxiety disorders, OCD, and BDD [43, 61]. First, the predominant cognitive and behavioral symptoms of these conditions (e.g., acquiring and maintaining possessions, hair pulling, skin picking) are often not experienced as intrusive or unwanted. Rather, they occur for a diverse number of affective or cognitive motivations (e.g., gratification, boredom, anger, not-just-right feelings) [34, 62]. For this reason, symptoms may be experienced as positive and reinforcing, neutral and automatic, or distressing and intrusive. There is thus a large degree of heterogeneity in the functional relationships between symptoms in hoarding disorder, HPD, or SPD, which aligns with empirical findings that these conditions may, in some cases, be better conceptualized with addictive, tic, or impulse spectrum disorders [10, 44, 63, 64]. As such, person-specific, functional assessment of symptoms is critical in clinical settings. Of note, distress in these conditions often presents due to attempts to stop or reduce the behavior (e.g., to dispose of items, pick skin less frequently) or from related impairment (e.g., resulting medical conditions, interpersonal conflicts), rather than a functional antecedent of the behavior.

First, in the cognitive-behavioral model of hoarding disorder [65], it is proposed that maladaptive beliefs about one's possessions (e.g., about their potential value in the future) as well as about discarding them (e.g., "What if I make a mistake and need this item later or am responsible for wasting it?") underlie hoarding symptoms. However, unlike OCD and BDD, such beliefs contribute not only to negative emotions such as sadness/grief, anxiety/fear, and guilt/shame but also positive emotions about acquiring and maintaining possessions (e.g., pleasure, pride). Thus, acquiring and difficulty discarding are maintained not only by negative reinforcement (e.g., avoiding unpleasant emotions by choosing to save an item) but also positive reinforcement (i.e., adding something rewarding that leads to an increase in the behavior; e.g., pleasure and excitement about retaining one's possessions). In addition, individuals with hoarding disorder present with information processing deficits (e.g., in memory, decision-making, etc.) [66, 67] that are uniquely considered in the conceptual model of hoarding.

Similarly, a broader range of functional motivations for hair pulling and skin picking have been implicated [68, 69]. Again beliefs about hair pulling and skin picking can contribute to the development and maintenance of symptoms including beliefs about one's inability to tolerate or control urges to pick/pull (e.g., "I can't stand having this gray and wiry hair on my head"), about the benefits of pulling/picking (e.g., "I need to pick my skin in order to be able to concentrate"), permission giving thoughts (e.g., "I'll just pull for 5 minutes and then stop"), and all/nothing beliefs (e.g., "I already messed up and started picking so I might as well keep going"). In addition, like compulsive rituals in OCD and BDD, individuals may engage in hair pulling or skin picking as a maladaptive emotion regu-

lation strategy aimed to reduce or alleviate generalized distress (e.g., feeling bored or anxious) or from thoughts and feelings of disgust, imperfection, or not-just-right experiences regarding one's hair or skin (e.g., searching for a gray or coarse hair that does not belong). However, hair pulling and skin picking may also generate and be reinforced by positive affective experiences, and it is not uncommon for individuals to have mixed feelings about their pulling/picking behaviors. For instance, while clients may be distressed by the loss of their hair or damage to their skin, they may also report gratification and pleasure when engaging in hair pulling and skin picking that maintain the behavior [64]. Finally, in some instances, hair pulling and skin picking may not be clearly linked to specific cognitive-affective motivations and may present as a more automatic behavior (i.e., pulling/picking without conscious awareness).

Therefore, due to the functional differences in the conceptual models of hoarding, HPD, and SPD, differential approaches for conceptualization and treatment are necessary (e.g., skills training for decision-making in hoarding) and will be discussed in Treatment Implications below.

Considerations for Assessment and Diagnosis

The significant overlap between anxiety disorders and OCRDs can confer additional challenges for the assessment and differential diagnoses of these conditions. Accurate diagnosis and comprehensive functional assessment of these disorders are necessary to select optimally efficacious treatment approaches and to tailor such treatments appropriately. In this section, specific methodologies and approaches for conducting such an assessment are outlined.

Functional Assessment

Across anxiety-related conditions and OCRDs, it is necessary to conduct a comprehensive assessment of the form and function of person-specific symptoms to indicate appropriate diagnosis and treatment [42, 69–72]. Particularly in OCRDs, there are a countless number of ways in which central cognitive (e.g., the content of intrusive thoughts or bodily concerns) and behavioral (e.g., safety behaviors implemented to reduce anxiety) symptoms present. Given this heterogeneity, it is critical to understand exactly *what* symptoms are present for a given individual and *how* those symptoms interact and function to maintain the individual's broader network of psychopathology. Specifically, several symptom domains are important to consider: (1) antecedents (i.e., cues/triggers), (2) behavioral symptoms and consequences (e.g., rituals, avoidance, and safety behaviors), and (3) interpersonal factors (e.g., family or partner accommodation, relationship distress).

Cues/Triggers

A multitude of external (e.g., situations, activities, objects, etc.) and internal (e.g., thoughts, emotions) antecedents may trigger OCRD symptoms. Thus, a comprehensive functional assessment should begin by obtaining a complete list of cues/triggers to aid in developing a cognitive-behavioral treatment plan (e.g., exposures to feared stimuli, habit reversal training). First, across OCRDs, certain external situations, activities, objects, or places may trigger symptoms. For instance, symptoms may be triggered by seeing a potential weapon or using a public restroom (OCD), seeing one's image in the mirror or being in locations like the gym or the beach (BDD), seeing an item on sale at the grocery store or receiving a new stack of mail (hoarding disorder), or using tweezers or talking on the phone (HPD/SPD). Assessing each of these external triggers, therefore, provides clinicians with treatment targets to help clients manage these challenging situations.

Internal experiences can also serve as potent triggers. First, as noted in the cognitive-behavioral model of OCRDs, cognitions play a role by triggering affective reactions (e.g., anxiety, disgust, or guilt/shame). Internal triggers can include intrusive images or doubts about being responsible for harm such as causing a fire (OCD), thoughts about how deformed a body part is (BDD), fears of losing important things and beliefs such as "I might need this one day" (hoarding disorder), and perfectionistic cognitions or rationalizations about pulling/picking (HPD/SPD). Second, although most commonly considered in anxiety disorders such as panic disorder, bodily sensations and emotional reactions can also serve as internal cues among the OCRDs including anxiety-related sensations interpreted as inappropriate, unwanted sexual arousal in OCD, physiological tension or boredom leading to hair pulling, or a tactile sensation (e.g., skin crawling) leading to skin picking.

Behavioral Symptoms and Consequences

Compulsions/Rituals Compulsions represent a unique behavioral symptom of OCRDs (which map onto other safety behaviors in other anxiety disorders). As previously described, compulsions may present as overt (e.g., external, observable behaviors) or covert (internal, mental rituals), and covert rituals can be more subtle and difficult to recognize or assess. Further, compulsions may be used before, during, or after being exposed to a feared stimulus in order to prevent, neutralize, escape, or eliminate a feared outcome or perceived wrongdoing.

In OCD, compulsions are most often functionally linked to obsessions along the four symptom dimensions discussed (e.g., fears about causing harm and checking, concerns about becoming ill and repeated washing, not-just-right feelings and ordering or counting, unacceptable thoughts about taboo topics and repeated attempts to replace thoughts with "good" ones) [4]. However, it is important to ensure that one understands the specific link between an individual client's compulsions and their fears (e.g., are they washing their hands because they fear them-

selves getting sick or others; are they checking the locks on their front door because they fear theft or an attack). In BDD, rituals may be both directly targeted to *change* physical appearance (e.g., time-consuming makeup routines, repeated medical procedures) or to reduce distress induced by appearance-related thoughts (e.g., seeking reassurance about physical appearance, checking the mirror). Further, compulsions in BDD may also overlap with symptoms of other OCRDs (e.g., hair pulling, skin picking) or eating disorders (e.g., eating or exercise rituals aimed to change perceived defects in weight/shape), and it is thus helpful to fully assess the purpose of these behaviors in clarifying appropriate diagnoses and treatment.

As highlighted throughout this chapter, it is necessary for the clinician to assess both the *types* of compulsions present for a given client and the *purpose* of these compulsions; that is, how is the compulsion linked to feared stimuli and obsessions, and why does the individual feel driven to engage in compulsions (e.g., what about the ritual feels better to do it this way, or what do they fear will occur if they *refrain from* engaging in the compulsion?). Such questions are critical to understanding the nature of the individual's symptoms, as well as for pinpointing how to design and implement evidence-based techniques to be most useful for an individual.

Hair-Pulling and Skin-Picking Behaviors As with OCD and BDD, it is useful for clinicians to gather detailed information about the form and function of hair-pulling and skin-picking behaviors, including detailed information about the pulling/picking behaviors themselves (e.g., what parts of the body individuals pick/pull from, a description of each step in the process), the individual's experience of what happens if they try to resist performing the behavior, as well as emotions or thoughts the individual experiences before, during, and after picking/pulling (e.g., loss of control, embarrassment, shame, relief, pleasure). It can be especially useful, given the guilt and shame clients feel about their hair-pulling or skin-picking behaviors [73], to normalize both the positive and negative aspects of picking or pulling so that clients feel more comfortable in disclosing their symptoms.

Avoidance Avoidance is a hallmark feature and often a primary maintaining factor of symptoms across anxiety-related conditions and OCRDs. Most individuals with these disorders will engage in avoidance in an effort to prevent feared internal or external triggers and other symptoms. The avoidance may be behavioral or experiential (e.g., avoidance of internal experiences like strong emotions or physical sensations) [74, 75] and as such may be overt or covert. First, across the OCRDs, a diverse array of specific situations or activities (e.g., being at parties in BDD, using cleaning products in OCD, discarding items in hoarding disorder, going swimming where others may see hair loss in HPD), places (e.g., public transportation, hospitals, public restrooms), people (e.g., homeless individuals, attractive individuals), or other objects or behaviors (e.g., saying certain words, taking photographs) may be avoided. Further, avoidance of internal experiences can be subtle and thus difficult for both the individual and the clinician to identify. Such internal avoidance efforts may include efforts to suppress, distract, or "white knuckle" to avoid experiencing

feared emotions or sensations. As discussed, avoidance serves as one of the primary maintaining factors of anxiety and OCRD-related symptoms by impeding naturalistic corrective learning and opportunities for the individual to be exposed to experiences that challenge and change core dysfunctional beliefs that underlie symptoms. As such, it is necessary to assess the breadth of *forms* maladaptive avoidance is taking, as well as the *function* of each avoidance behavior in relation to other symptoms: what does the avoidance behavior look like, how is it causing interference, and what is it accomplishing or preventing?

Interpersonal Factors

Finally, it is critical to assess the extent to which environmental contexts and interpersonal factors are contributing to symptom severity and maintenance. Across anxiety-related conditions, symptom *accommodation* by loved ones is very prevalent [76]. Specifically, well-intentioned family members, partners, or close friends often contribute to the maintenance of symptoms by engaging in avoidance, safety behaviors, or rituals (especially in OCD and BDD) with or for the individual. Family may also develop independent patterns of avoidance aimed to prevent or reduce the chance of their loved one becoming anxious, particularly if they themselves become highly upset by their loved one's distress or symptoms. Although intentioned to support their loved ones, these behaviors paradoxically contribute to the maintenance and exacerbation of symptoms. Further, patterns of accommodation (e.g., assisting a client with OCD with checking rituals to ensure that doors are locked, providing reassurance repeatedly to a client with BDD that their hair looks fine) can facilitate relational distress over time. Comprehensively assessing the ways in which interpersonal dynamics are contributing to symptoms is thus essential for informing either individual- or couple-/family-based (where possible) treatment approaches to target core symptoms and maximize treatment gains [77, 78].

Empirically Validated Assessment Measures

Clinician-Administered, Structured Interviews

There are three structured clinical interviews that have been updated for the diagnosis of DSM-5 anxiety disorders and OCRDs: the Anxiety Disorders Interview Schedule for DSM-5 (ADIS-5) [79], the Structured Clinical Interview for DSM-5 (SCID-5) [80], and the Mini-International Neuropsychiatric Interview, version 7 (MINI) [81]. In addition, several clinical interviews have been empirically validated for more fine-tuned assessment of specific OCRDs. Due to the heterogeneity of symptom presentations in OCRDs, these assessments are particularly useful for enriching case-specific conceptualizations and informing treatment planning.

Anxiety Disorders Interview Schedule for DSM-5 (ADIS-5) The ADIS-5 is a semi-structured, clinician-administered interview for anxiety and related disorders [79]. The ADIS-5 facilitates differential diagnostics across anxiety, OC, trauma- and stress-related, mood (e.g., depression), and somatoform disorders (e.g., illness anxiety disorder). Given the high rates of comorbidity within and between anxiety and OCRDs, as well as with other forms of psychopathology (e.g., substance use, depression), such an assessment is particularly useful.

In line with the demand for more dimensional methods of assessment and diagnosis, the ADIS-5 can assess central, common features of psychopathology in a dimensional fashion (e.g., assessing severity from 0 to 8 rather than the dichotomous presence or absence of symptoms). Further, the clinician can gather data regarding the functional nature and specific manifestation of symptoms (e.g., situations avoided, content of anxiety cognitions). The ADIS has strong reliability and specificity in identifying certain diagnoses [82]. The main limitation of the ADIS-5 is that it can be particularly time-consuming. However, specific modules may be utilized as needed for a more efficient assessment (e.g., of OCD).

Structured Clinical Interview for DSM Axis I Disorders (SCID-5) The SCID-5 is also a semi-structured interview, typically administered by a clinician, with good psychometric support [83, 84]. The SCID provides a more comprehensive and inclusive assessment of DSM-5 disorders. However, qualitative information on the person-specific presentation of symptoms is lost. As such, the SCID may be best used as an initial assessment of psychiatry history and followed by more specific, detailed assessments of present diagnostic concerns.

Mini-International Neuropsychiatric Interview (MINI) The MINI is a brief, structured interview that, similar to the SCID, assesses the presence of DSM diagnoses [81, 85]. The MINI can be administered in 15–20 minutes and thus provides a highly time-efficient option. Further, the MINI has similar validity and reliability to the SCID [86]. However, given its brevity, this measure may best be administered for brief screening (e.g., to rule in/out diagnoses) in tandem with clinician-administered or self-report measures that provide more detailed information.

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) The Y-BOCS is the gold standard interview assessment of OCD symptom severity [87]. The measure provides a comprehensive checklist to assess the primary obsessions and compulsions which will serve as core targets for treatment. Questions assess the time occupied, interference, distress, resistance, and degree of control for both obsessions and compulsions (assessed separately). Supplemental questions assess insight, as well as the severity of common features in OCD (e.g., avoidance, inflated responsibility, doubting) that may be important treatment considerations. The Y-BOCS demonstrates good validity and reliability and can be administered and scored with relative ease [88, 89].

Although the Y-BOCS provides specificity regarding symptoms, it fails to capture functional relationships among symptoms that are critical to identify and target in treatment. Specifically, obsessions and compulsions are assessed as distinct from one another, and the links between the individual's obsessions (e.g., about causing harm to one's family) and compulsions (e.g., repeatedly checking the stove and locks) are not assessed. It also does not equally capture the full spectrum of OCD symptoms (e.g., mental rituals are underrepresented) and consists of items (e.g., compulsive self-harm, hair pulling, eating behaviors) that may contribute to misdiagnosis without sufficient training.

The Y-BOCS has been adapted for the assessment of BDD (BDD-YBOCS) [90] and hair pulling (Yale-Brown Obsessive-Compulsive-Scale-Trichotillomania; Y-BOCS-TM) [91]). Additionally, it has been adapted for SPD, although psychometric data for this modification is lacking (The Yale-Brown Obsessive-Compulsive Scale for Neurotic Excoriation; YBOCS-NE [92]). Overall, the structure of these additional versions is similar to original Y-BOCS, and the symptoms assessed have been modified for the primary symptoms of BDD, HPD, and SPD.

Hoarding Rating Scale-Interview (HRS-I) The HRS-I is a commonly used and validated clinical interview to assess hoarding symptoms [93]. The measure is brief (five items), is easy to administer, and assesses the severity of clutter, excessive acquisition, difficulty discarding, distress, and impairment. The HRS-I demonstrates strong internal consistency, reliability, and validity [94] and has cut scores for use in clinical and nonclinical populations. Of note, the measure does not collect qualitative information necessary for a comprehensive case conceptualization (e.g., specific content of symptom-related cognitions, level of insight).

Trichotillomania Severity Scale (TSS) The TSS was created by the National Institute of Mental Health (NIMH) [95] and has been used to monitor hair-pulling severity [96]. The TSS was developed based on the Y-BOCS-TM and consists of five items that assess the duration, impairment, distress, resistance, and control of HPD symptoms. Psychometric validation of the TSS is not available.

Self-Report Measures

A number of self-report assessments are available and psychometrically validated for the assessment of OCRDs. The focus of this section is on OC-specific measures, but given the high rates of comorbidity and conceptual overlap between anxiety and OCRDs, transdiagnostic self-report assessments may also be useful (e.g., Overall Anxiety Severity and Impairment Scale, OASIS [97]). Overall, self-report assessments provide a quick, accessible, and structured way to assess initial symptoms and track symptom severity over the course of treatment.

Dimensional Obsessive-Compulsive Scale (DOCS) The DOCS consists of 20 items, divided into 4 subscales that correspond to OC symptom dimensions consistently identified and discussed above: (a) contamination, (b) responsibility for harm and mistakes, (c) symmetry/ordering, and (d) unacceptable thoughts [98]. Given

symptom heterogeneity in OCD, each subscale details examples of obsessions and compulsions that highlight the *form* and *function* of intrusive thoughts, rituals, and avoidance. For each subscale, five items are completed to assess the severity of symptoms (over the past month). Given empirical support for conceptualizing the mechanisms and treatment of OCD based on symptom dimensions, the DOCS is best scored and interpreted based on its subscales [4, 17]. The DOCS subscales have demonstrated excellent reliability (α = 0.94–0.96) and validity [98].

Body Dysmorphic Symptom Scale (BDD-SS)   The BDD-SS assesses the presence and severity of BDD symptoms across seven symptom clusters: (1) checking, (2) grooming, (3) behaviors aimed to change weight or shape, (4) hair pulling/skin picking, (5) avoidance, (6) medical behaviors (e.g., surgery), and (7) cognitive symptoms [99]. The BDD-SS can be summed for an overall symptom severity rating, or a composite score of the quantity of symptoms present can be generated (range 0–54). Preliminary psychometric results provide excellent support for the BDD-SS [99], and it demonstrates robust change to treatment [100–102].

Saving Inventory-Revised (SI-R)   The SI-R is a measure of hoarding symptom severity, which consists of 26 items that assess hoarding symptoms along 3 conceptually meaningful subscales: difficulty discarding, acquisition problems, and excessive clutter [37]. Psychometric data supports good internal consistency and reliability for the SI-R [37, 103]. The SI-R demonstrates strong divergent validity (i.e., low correlations with measures of OCD symptom severity), suggesting it may be useful for distinguishing between these two conditions.

Skin Picking Scale (SPS)   The SPS is a brief measure that assesses SPD severity with six items that assess the (1) frequency of urges to engage in skin picking, (2) intensity of these urges, (3) time spent picking, (4) picking-related interference, (5) distress associated with picking behavior, and (6) avoidance [104]. The SPS is used as an index of clinical severity, with a clinical cutoff of 7. The SPS has good psychometric support [104]. The SPS may be coupled with the Skin Picking Impact Scale (SPIS), which is a 28-item assessment of functional consequences associated with SPD [105, 106].

Massachusetts General Hospital Hairpulling Scale (MGH-HPS)   The MGH-HPS is a brief (seven items) measure of the severity, frequency, and distress associated with hair pulling [107]. The MGH-HPS demonstrates good internal consistency, reliability, and validity [108, 109]. Further supporting its utility, the MGH-HPS is sensitive to symptom change in effective treatments for HPD [110, 111].

Differential Diagnosis

As illustrated in the initial sections of this chapter, anxiety and OCRDs share both considerable overlap and several critical distinctions. In order to best devise an evidence-based treatment plan for a given individual, it is necessary to comprehen-

sively assess and accurately diagnose the psychological conditions present. This process often involves differentiating between anxiety, OCRDs, and related disorders, to arrive at the most accurate conceptualization of the individual's presenting concerns. For example, within OCRDs several specific behavioral symptoms (e.g., hair pulling) appear in multiple different diagnoses (e.g., BDD, HPD). However, the function of the symptom and its context within the broader network of symptoms will lead to different diagnoses and empirically supported interventions (e.g., exposure vs. habit reversal training). It is also often the case that anxiety, OCRDs, and related conditions (e.g., depression, eating disorders, substance use disorders) co-occur [5], in which case delineating which condition(s) are *primary* (i.e., central to presenting concerns, distress, or impairment; motivating treatment seeking) as well as identifying all conditions that are current sources of distress can be important for ordering and integrating of evidence-based treatment approaches.

In the following section, we will thus discuss specific considerations for differentiating within OCRDs and between OC and anxiety spectrum disorders that demonstrate significant overlap in symptom presentation or function. We will focus on specific distinctions that tend to be most challenging or relevant to clinical practice.

Within OC Spectrum Disorders

OCD vs. BDD   Given the overlap in the form and function of symptoms between OCD and BDD [112], these diagnoses are sometimes misdiagnosed. In both cases, central symptoms involve intrusive, distressing thoughts and rituals aimed to reduce anxiety (as well as disgust, guilt/shame). Perhaps most important to this diagnostic distinction is the *content* of intrusive thoughts and symptoms. In OCD, the topics of intrusive thoughts can be quite diverse. In BDD, on the other hand, the content of intrusions, distress, and associated compulsions is more restricted and revolves specifically around the perception of a physical defect in one's appearance. BDD and OCD often co-occur [33] and share many risk and maintenance factors; as such, an individual with obsessions and compulsions both about physical appearance and other obsessional fears (e.g., contamination concerns) should be diagnosed and treated for both conditions.

BDD vs. Hair-Pulling and Skin-Picking Disorders   A particularly difficult challenge can be differentiating between BDD and HPD or SPD, given the potential for symptoms of hair pulling or skin picking to present in either condition. In BDD, individuals may engage in hair pulling or skin picking as rituals in order to alleviate distress associated with a perceived problem with the appearance of one's hair, skin, or other physical concerns [113]. In this way, the behavior is functionally linked with other primary BDD symptoms, such as the cognitive (e.g., intrusive thoughts about one's appearance) and affective (e.g., anxiety, disgust) responses. However, in HPD or SPD, the hair pulling or skin picking, respectively, represents the core symptom of the disorder. Furthermore, the behavior is not motivated by a desire to change one's appearance in HPD and SPD and may not be specifically tied to particular cognitions. In HPD and SPD, symptoms are

also often motivated and reinforced by gratification, relief, or other positive affective experiences not present in the context of BDD obsessions or rituals.

Between OC Spectrum and Anxiety-Related Disorders

Distinguishing between anxiety disorders and OC spectrum disorders can present a particular challenge for clinicians, particularly given the overlap in the form and function of symptoms [2]. Overall, in order to diagnose OCD, obsessions must not focus on content that is better characterized by an anxiety disorder (e.g., generalized anxiety disorder, social anxiety disorder, panic disorder, specific phobias). For example, intrusions that solely involve concerns regarding finances, work, and relationships are characteristic of generalized anxiety disorder. Those that focus exclusively on fears of judgment, embarrassment, humiliation, or causing offense to others in social contexts would be an indication of social anxiety disorder. Additionally, intrusive thoughts about catastrophic consequences of physical sensations (e.g., "I might be dying," "I am having a heart attack," "I could lose control") and help not being available or escape being difficult if one were to have a panic attack (e.g., in open spaces, public transportation) are symptomatic of panic disorder and agoraphobia, respectively. Finally, in specific phobias, fear is elicited by a circumscribed stimulus (e.g., dogs, spiders, airplanes).

For all of these cases, intrusions of a similar nature or content may occur in OCD. However, intrusive thoughts in OCD are typically *egodystonic*, meaning that obsessions (e.g., about causing harm, blasphemous unacceptable thoughts) actively contradict one's values, moral code, or identity [114]. This is in contrast to other anxiety-related disorders. For example, an individual with generalized anxiety disorder who is concerned about doing well in school may worry about whether she has studied enough for her upcoming exam; thus, these worries about studying are in line with her image of herself as a hardworking student. In contrast, an individual with OCD might experience obsessions about whether he plagiarized on a research paper without meaning to; accordingly, these obsessions about cheating are contrary to his sense of self. Additionally, intrusions in OCD often involve irrational or impossible fears (e.g., contracting HIV from using a public restroom, causing a family member to die if a prayer is not said perfectly). In contrast, in anxiety disorders, intrusions are more likely to be about realistic or real-world problems (e.g., health, work performance), and individuals are less likely to endorse that intrusions are irrational [115]. Given the overlap in risk factors for OCD and anxiety disorders, it is very common for OCD and anxiety disorders to co-occur [116, 117]. As such, if cognitive symptoms consist of multiple, cross-diagnostic content domains (e.g., intrusive cognitions about daily concerns such as finances and relationships as well as about causing harm to loved ones), it is an indication of more than one anxiety-related disorder (i.e., comorbidity).

Social Anxiety Disorder (SAD) vs. BDD BDD can share significant symptom overlap with SAD in particular (e.g., fears around negative evaluation from others,

avoidance of social setting such as parties, crowds, or eating in public) [118]. Importantly, in BDD, central cognitions involve fear of judgment or negative evaluation from others specifically about the perceived bodily defect, whereas in SAD such fears will more generally pertain to performance, competence, etc. As described, assessing the specific content of cognitions and motivations linked with one's behaviors can be very helpful for informing such nuanced distinctions and directing treatment accordingly.

PTSD vs. OCD PTSD can be distinguished from OC spectrum conditions, in that fear responding is based on a discrete event that *did occur* (i.e., criterion A trauma), whereas symptoms in OCRDs are typically based on a feared outcome that has not actually occurred (and is highly unlikely) [1]. Although symptoms of PTSD overlap with OCD, including distressing, intrusive thoughts, avoidance, and safety behaviors, there are also unique symptoms, such as re-experiencing (e.g., flashbacks, nightmares). Moreover, certain central affective symptoms in PTSD are not often seen in OCD (e.g., anger, anhedonia, dissociation).

Although less common, one important consideration is post-traumatic presentations of OCRDs [119–121]. Often PTSD symptoms may be primary; for example, following a traumatic sexual assault, an individual may develop decontamination compulsions (e.g., repeated washing aimed to reduce intrusive thoughts about the trauma) in addition to other PTSD symptoms like nightmares and hypervigilance. For this individual, trauma-focused treatment may be most efficient and effective and would likely reduce compulsive behaviors. However, in other cases, contamination symptoms may generalize to more broad concerns that remain after acute post-traumatic symptoms resolve and are no longer linked solely to the trauma. In these cases, evidence-based treatments for OCD may be more effective. Given the shared cognitive, behavioral, and affective risk factors implicated in anxiety-related conditions, lifetime comorbidity between OCRDs and trauma-related disorders is common [21, 33, 122]. For this reason, it is important to assess whether OCD preceded the traumatic event, as this distinction can inform the conceptualization of an individual's presentation and the most appropriate approaches or targets for treatment.

Illness Anxiety Disorder (IAD) vs. OCD IAD (previously known as hypochondriasis or health anxiety) is a somatoform disorder in which individuals excessively worry about becoming ill (e.g., catastrophically misinterpreting benign physiological symptoms as a serious medical condition) [1]. In response to concerns about illness, individuals with IAD engage in safety behaviors (e.g., excessive reassurance seeking from medical providers, repeatedly checking for signs of illness) and avoidance (e.g., of certain people or places associated with illness such as hospitals) [123]. In this way, the symptoms of IAD can overlap with those that present in OCD (e.g., contamination-related obsessions and compulsions). Further, they serve a similar function in the maintenance of impairing distress. IAD can best be distinguished from OCD based on the narrow scope of symptom content [124]. In the case of IAD, symptoms exclusively focus on disease-related

concerns (e.g., having cancer, heart disease, etc.). In contrast, individuals with OCD often have more broad concerns than solely illness/disease (e.g., germs in raw meat, chemicals in cleaning products, disgust from feces). Lastly, OCD can involve more irrational or even impossible fears (e.g., becoming blind from coming into contact with someone who is blind).

Treatment Implications: Diagnostic-Specific and Transdiagnostic Considerations

Considering Comorbidity

As highlighted throughout, comorbidity presents as the rule rather than the exception across OCRDs. Often, anxiety disorders and OCRDs co-occur with one another as well as with other functionally related conditions (e.g., substance use disorders, depression). A deeper discussion of comorbidity in anxiety-related disorders can be found in Chap. 5. However, we briefly highlight how comorbidity impacts treatment approaches for OCRDs.

First, depression is very common among the OCRDs [125]. When depression is particularly severe, it may merit acute and focused intervention prior to treating other OCRD symptoms. However, depression may often arise from the impairment and avoidance that results from OCRDs (e.g., a client with OCD who engages in time-consuming shower rituals or a client with BDD who can't leave the house). In such cases, depression may naturally abate in evidence-based interventions targeting the primary OCRD condition. Finally, in some cases anxiety and depression may be closely entangled, and it may be difficult to distinguish one condition as primary. For individuals with this presentation, combined or sequential, evidence-based interventions may be useful (e.g., integrating behavioral activation into cognitive-behavioral treatments for OCRDs, combining antidepressants and cognitive-behavioral therapy [CBT]). Although various empirically supported psychological and pharmacological treatments exist for anxiety and depression, limited research has been conducted to identify the optimal sequencing or combination of these approaches for comorbid cases. As such, the acceptability of interventions for a given client, the case conceptualization, and empirically informed clinical judgment should be used to devise the most useful treatment plan. Regular assessment (e.g., of primary symptoms) can be used to modify this plan as needed.

A second important consideration is the comorbid presentation of substance use disorders, which may emerge as a maladaptive coping strategy used to regulate the distress an individual is experiencing due to OCRD symptoms [126]. Similar to clinical considerations for depression, the acute risk associated with the substance use may serve as the primary distinction of appropriate care. For example, if substance use is severe or poses a significant medical risk (e.g., overdose, alcohol withdrawal), it may warrant inpatient or intensive outpatient services in order to assist

the individual in achieving a medically stable or abstinent state. Moreover, due to the physical and cognitive impacts of substance use, it is necessary to achieve sufficient control over the substance use behavior (e.g., sobriety for therapy sessions) in order for the individual to benefit from psychological interventions. Additionally, collaboration with medical providers may be necessary (e.g., primary care physicians) to ensure client safety and appropriateness for therapy. However, in many cases substance-related comorbidities may be subthreshold or secondary to the OCRD. For such individuals, these symptoms may abate by treating core, underlying mechanisms (e.g., improving coping skills, distress tolerance). Moreover, research suggests that integrating treatment to directly target both substance use and OCD symptoms concurrently may be most effective [127].

Frontline Psychological Treatment: Cognitive-Behavioral Techniques

Cognitive-behavioral approaches are the leading, evidence-based techniques for the treatment of both anxiety disorders and OCRDs [128]. As follows, given the historical and conceptual overlap between anxiety disorders and OCD, the theory and guiding principles of CBT are the same. Moreover, the support for the efficacy of CBT for OCD (as well as BDD, though less research has been done) largely mirrors that of anxiety disorders [129]. For this reason, our discussion of treatment will focus on the specifics and nuances of CBT for OCRDs, including the empirical evidence and applied use of CBT techniques for OCD and BDD, as well as the distinctions for hoarding, HPD, and SPD. A detailed discussion of the history, theory, and principles of CBT for anxiety can be found in Chap. 12.

Across anxiety disorders, and several OCRDs, two principle components of CBT appear effective: exposure and cognitive therapy. These approaches may be administered independently or integrated. Of note, in behavioral therapy, cognitive techniques are often used (e.g., in the processing of exposure exercises) [52]. Similarly, behavioral experiments (i.e., exposures to test the validity of beliefs) are often included in cognitive therapy.

Psychoeducation and Self-Monitoring

Of note, as with anxiety disorders, effective treatments for OCRDs typically begin with psychoeducation and self-monitoring [130]. These initial components of treatment are essential to allow the client to understand the cognitive-behavioral conceptualization and the usefulness of practicing therapeutic exercises (e.g., self-monitoring, exposure). These initial components may be especially helpful for individuals with lower insight into the nature or impairment associated with their symptoms, which presents more often in OCRDs than anxiety disorders.

Psychoeducation for OCRDs stems from the functional assessment of symptoms. Clinicians orient the client to the overall CBT model of their presenting concerns and work collaboratively to identify ways in which the model extends to his/her symptoms. The clinician then builds upon this formulation to discuss the utility and effectiveness of CBT exercises in the context of this model and highlight treatment targets for the individual. This component of treatment is particularly important for motivating clients to engage in challenging therapeutic work by ensuring that individuals understand the rationale for such challenging exercises and their relevance to the particular sources of anxiety and impairment in their lives.

Self-monitoring is a critical component of CBT and consists of between-session, self-reported assessments of cognitive, behavioral, and affective symptoms and relevant contextual experiences. Individuals are asked in the beginning, and throughout treatment, to monitor their symptoms (e.g., rituals in OCD/BDD, hair pulling/skin picking) as well their antecedents (i.e., triggers) and consequences. Self-monitoring can be used to progressively refine the case conceptualization and treatment plan accordingly. It also teaches the client to identify symptoms in the moment as they arise and to develop greater self-awareness. In this way, self-monitoring can facilitate a more robust self-conceptualization of symptoms, including greater insight into the causal links between symptoms, their triggers, and their relationships to impairment.

Cognitive Therapy

In cognitive therapy, various techniques (similar to those for anxiety disorders) are used to challenge the maladaptive beliefs that contribute to and maintain symptoms of OCRDs: thought challenging and behavioral experiments [131]. First, thought challenging exercises have similar targets and mechanisms for OCRDs as anxiety disorders. For OCD, thought challenging often targets themes including the overestimation of personal responsibility for harm, the importance and need to control thoughts, or the need for perfection and order [132]. For example, therapist and client might use a pie chart to examine all the possible factors that could be responsible for a feared outcome (to challenge overestimates of responsibility). Of note, the research is mixed as to whether conducting cognitive restructuring before beginning exposure is necessary [133, 134]. In BDD, cognitive techniques are more standard practice and involve specific focus on cognitive restructuring of body dysmorphic beliefs about appearance and the self (e.g., "If I looked better, my whole life would be better") [113].

Although results for cognitive therapy in hoarding are less robust [42, 135], thought challenging can be useful and involves examining core beliefs regarding the importance of acquiring or saving items and one's ability to tolerate discarding items [136]. Given that the CBT formulation of HPD and SPD differs, CBT typically focuses more on behavioral components (e.g., habit reversal, described below). However, some evidence suggests thought challenging may be useful specifically for challenging transdiagnostic factors linked with symptoms, such as

firmly held beliefs about the need for perfectionism as well as examining cognitions that may maintain pulling/picking for an individual (e.g., permission-giving thoughts) [137].

Finally, behavioral experiments aim to further cognitive restructuring to provide real-life opportunities to challenge unhelpful or inaccurate beliefs. As such, the effectiveness and approach to behavioral experiments parallel that described for exposure below.

Exposure and Response Prevention

Exposure is a core component of effective treatment for anxiety-related conditions and OCRDs, including OCD, BDD, and to some extent hoarding [113, 125]. In exposure, individuals test their primary fears and challenge distorted cognitions in imagined and real-life experiences. Exposures are informed by the person-specific, functional assessment and can be tailored to address a client's specific feared outcomes. For this reason, exposure for OCRDs largely maps onto that described for anxiety disorders. Clinicians and clients collaboratively work together to identify the anticipated severity of distress associated with different triggers in a fear hierarchy. Traditionally, exposures for anxiety-related disorders have relied upon on a gradual, sequential implementation of exposures [138]; however, recent research suggests that selecting exposure intensity in a varied fashion may provide additional gains by further challenging intolerance of uncertainty (common among individuals with anxiety-related conditions) and bolstering self-efficacy (i.e., by implying that an individual is ready and able to handle even more challenging exposures) [139, 140]. Further, variety in exposure intensity more closely aligns with the way in which challenges and fear stimuli are encountered in real life and as such may aid in the generalization of therapeutic gains. Thus, clinicians and clients can choose the order in which they conduct exposure exercises based on the client's goals. Of note, as described in greater detail for anxiety disorders (Chap. 12), even with varied intensity approaches, it is necessary to assure that exposures are designed for early and continued success in order to cultivate self-efficacy and mastery, as well as protect against symptom worsening or early dropout.

Taken together, exposure can serve many important functions in the treatment of anxiety and OCRDs. First, in line with the emotional processing theory of anxiety disorders [141], exposure can facilitate habituation, or gradual decreases in anxious responding, to the fear stimulus. In the case of OCD, for example, this might involve remaining in contact with a feared, contaminated item (e.g., public restroom toilet) for as long as it takes for anxiety to habituate. Importantly for OCRDs, individuals do not engage in compulsions during this extended period of time (i.e., response prevention), which allows fear to naturally abate without rituals or avoidance (similar to eliminating safety behaviors in the treatment of anxiety). Exposure can also facilitate cognitive change, since the individual can test distorted beliefs via exposure and develop more accurate appraisals (e.g., of the likelihood and severity of a feared outcome such as getting sick).

For OCRDs, as with anxiety disorders, research has suggested that, although habituation may occur in the context of exposure, it is not necessarily predictive of long-term treatment outcome [139]. Moreover, an overreliance on habituation may incidentally reinforce maladaptive beliefs that anxiety and obsessions are intolerable and should be eliminated, which can be a source of symptom maintenance [140]. Thus, it may additionally be useful to emphasize the client's *willingness* or ability to handle the exposure when conducting these exercises. Given that anxiety is a natural emotional experience, clinicians can help clients set goals for exposure that emphasize distress tolerance. Indeed, due to patterns of avoidance and compulsions, individuals have limited opportunities to learn or apply adaptive coping behaviors and to accurately appraise their ability to manage distress in the context of fear triggers. As such, exposure provides an opportunity for the individual to take in more accurate information about their ability to sit with their emotions and associated physical sensations (e.g., the ability for a client with BDD to tolerate the distress from having their photograph taken). Thus, exposure goals focus on the *process* of the exercise (e.g., "Wow, that's terrific – you are staying in this even though it's uncomfortable"), over the outcome (e.g., habituation). This can help buffer against feelings of failure when exposures are challenging and anxiety may not decrease or for when feared occurrences do happen following exposure (e.g., an individual gets sick after a contamination exposure), using this as an opportunity to commend their efforts, to highlight whether the actual sickness is as bad as anticipated severity of illness, as well as their ability to tolerate the distress of their feared event occurring.

In applying exposure techniques to the various OCRDs, exposures in the context of contamination concerns in OCD, for example, might involve a client sitting on a toilet in a public restroom, touching door handles and elevator buttons, or sitting in a hospital waiting room where others may be sick. For each of these exercises, the client would aim to sit with feelings of being "dirty," test maladaptive beliefs that doing these activities will mean he will contract an illness/disease, and practice tolerating anxiety/distress. For an individual with BDD, hierarchy items might include leaving the house without wearing makeup (for skin-related concerns), wearing shorts (for leg-related concerns), wearing hair in a ponytail (for ear-related concerns), working with mirrors to support exposure (e.g., approaching physical features a client has been avoiding), and perceptual retraining (i.e., learning to describe one's whole body objectively and nonjudgmentally when looking in the mirror and shifting attentional focus away from the perceived defect). The therapist and client might aim to specify an amount of time, for instance, that the client estimates she can manage these activities (and test out whether she can exceed it).

Finally, for hoarding disorder, exposure exercises can also be designed around discarding items in the home as well as refraining from acquiring new possessions [136]. For example, discarding hierarchies might quantify anticipated distress if a client were to sort through mail and paperwork, discard old clothes, donate books, etc. Moreover, nonacquisition exposures can be designed for a client to spend time in a place that normally triggers acquiring (e.g., yard sale) and practice observing

and tolerating urges to acquire without purchasing anything. Of note, in treating hoarding disorder, these behavioral exercises are often preceded by skills training that addresses deficits that can interfere with discarding exercises including skills for sustaining attention, prioritizing tasks, organization and planning, and decision-making [65].

Habit Reversal Training (HRT)

HRT is one of the leading approaches implemented in CBT for HPD and SPD [142, 143]. HRT recognizes the unique cognitive-behavioral conceptualization of these phenomena and the importance of positive as well as negative affect and reinforcement to the maintenance of these concerns. HRT was derived from behavioral theory as well as neurological evidence regarding the acquisition, maintenance, and extinction of repetitive behaviors [144]. Moreover, it recognizes the potential for cognitive, affective, and contextual factors to trigger or exacerbate such behaviors. In this way, both the core behavioral mechanisms of HPD/SPD can be addressed, as well as individual factors (e.g., workplace stress, not-just-right experiences, perfectionism) that are linked with an individual's symptom presentation.

The components of HRT typically include self-monitoring, awareness training, competing response training, and motivational training [145]. In HRT, psychoeducation and self-monitoring are critical for the individual to become aware of urges to engage in hair pulling or skin picking in the moment, as well as their personal triggers and associated consequences for the behavior. Next, the focus shifts to developing and implementing competing, adaptive responses that prevent hair pulling or skin picking including relaxation training (e.g., mindfulness, breathing techniques) and other activities that reduce the urge to engage in or prevent the behavior from occurring (e.g., performing an alternate activity with one's hands like clenching fists). Motivational training is an important component of HRT, as clients often present with low intrinsic motivation to cease the behavior due to the rewarding aspects. Functional consequences noted in self-monitoring (e.g., interpersonal strain, medical care, skin damage) may be used to highlight the negative consequences of engaging in skin picking or hair pulling and thus motivate consistent engagement in HRT exercises. Further, given that these behaviors are often positively reinforced, it is critical to assure that alternative behaviors include rewarding experiences (e.g., replacing hair pulling with a soothing scalp massager).

HRT has been demonstrated to be a highly effective behavioral treatment approach for HPD and SPD [145] and common cognitive-behavioral elements are key to more comprehensive cognitive-behavioral approaches [146]. Additionally, promising new research demonstrates the utility of integrating technology to augment awareness training and the effectiveness of HRT. For example, a recent open trial demonstrated promising feasibility, tolerability, and efficacy of HRT augmented by a wearable device that alerted individuals of hand-to-head contact [147].

Promising Psychological Treatments

Recently, newer CBT-based approaches have been developed and shown promise for augmenting the treatment of OCRDs. These approaches consist of the unified protocol (UP) [148] and acceptance and commitment therapy (ACT) [149]. It is important to acknowledge that with both the UP and ACT, considerable research is still needed to provide evidence-based guidelines about which interventions and treatment components work best for whom and how these approaches can be optimally sequenced and tailored to the individual.

Unified Protocol (UP)

The UP was designed based on extensive empirical evidence implicating shared risk and maintenance factors in emotional disorders, such as anxiety disorders, OCD, and other mood-related disorders [150]. Transdiagnostic, skills-based modules include present-focused affective awareness, psychological flexibility, affective avoidance and maladaptive coping behaviors, tolerance of internal experiences, and exposure to distressing experiences and challenging emotion. Randomized controlled trials support the efficacy of the UP in reducing anxiety and depression symptoms [151, 152] as well as OCD symptom severity (e.g., 46% decrease in OCD severity, 83% qualified for responder status by follow-up) [152]. The UP has not be specifically examined for the other OCRDs, although its overlap with treatment targets for BDD suggests it may be helpful.

Acceptance and Commitment Therapy (ACT)

ACT is another promising treatment for OCRDs [153] that focuses on improving psychological flexibility and the tolerability of internal experiences such as obsessions (in OCD and BDD) and urges (in HPD and SPD). ACT techniques have been applied to specific OCRDs including OCD [154], body dissatisfaction [155], skin picking [156], and hair pulling [157]. ACT alone has shown initial evidence for the treatment of OCD [158, 159]. Additionally, a recent randomized controlled trial demonstrated that ACT-informed ERP demonstrated comparable effectiveness to ERP alone [160]. ACT has also shown promise for targeting body dissatisfaction among individuals with eating disorders [161, 162]. Finally, ACT combined with HRT may facilitate treatment gains (e.g., improved acceptance of urges to pick/pull) for HPD and SPD [157, 163]. Given the extant evidence, clinicians may choose to implement ACT in combination with other empirically supported techniques for OCRDs (e.g., exposures that focus on one's willingness to have unwanted internal experiences).

Conclusions

In summary, the OCRDs have symptom and conceptual similarities both among one another and with the anxiety disorders, with overlapping diagnostic criteria, cognitive-behavioral conceptualizations, and treatment approaches. However, the OCRDs also have notable heterogeneity and key distinctions (e.g., the differential diagnosis of PTSD vs. OCD, SAD vs. BDD) that inform the understanding and treatment of these problems. In particular, OCD and BDD are both characterized by anxiety-provoking repetitive thoughts and negatively reinforced compulsive behaviors that are centered around contamination, harm, taboo topics, and symmetry (as seen in OCD) and appearance-related concerns (as seen in BDD). Thus, such problems are primarily treated with cognitive-behavioral interventions (e.g., exposure therapy) that challenge maladaptive beliefs about threat (e.g., the overvaluation of appearance, the inability to tolerate distress) and allow clients to progressively face their fears. Hoarding disorder, HPD, and SPD are distinguished in that they are maintained by both negative and positive emotions and reinforcement that warrant unique treatment approaches (e.g., motivational techniques to address the pleasurable aspects of hair pulling and saving items, habit reversal training, and skills training to address informational processing deficits in hoarding disorder). Thus, clinicians who understand these nuances will be well-equipped to apply empirically supported principles flexibly to treat these patients.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (dsm-5®). Arlington: American Psychiatric Pub; 2013.
2. Abramowitz JS, Jacoby RJ. Obsessive-compulsive and related disorders: a critical review of the new diagnostic class. Annu Rev Clin Psychol. 2015;11:165–86.
3. Mataix-Cols D, Rauch SL, Baer L, et al. Symptom stability in adult obsessive-compulsive disorder: data from a naturalistic two-year follow-up study. Am J PsychiatryAm J Psychiatry. 2002; https://doi.org/10.1176/appi.ajp.159.2.263.
4. McKay D, Abramowitz JS, Calamari JE, Kyrios M, Radomsky A, Sookman D, Taylor S, Wilhelm S. A critical evaluation of obsessive–compulsive disorder subtypes: symptoms versus mechanisms. Clin Psychol Rev. 2004;24:283–313.
5. Richter MA, Summerfeldt LJ, Antony MM, Swinson RP. Obsessive-compulsive spectrum conditions in obsessive-compulsive disorder and other anxiety disorders. Depress Anxiety. 2003;18:118–27.
6. Wilhelm S, Otto MW, Zucker BG, Pollack MH. Prevalence of body dysmorphic disorder in patients with anxiety disorders. J Anxiety Disord. 1997;11:499–502.
7. Hollander E, Braun A, Simeon D. Should OCD leave the anxiety disorders in DSM-V? The case for obsessive compulsive-related disorders. Depress Anxiety. 2008;25:317–29.
8. Hollander E, Kim S, Khanna S, Pallanti S. Obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: diagnostic and dimensional issues. CNS Spectr. 2007;12:5–13.

9. Grant JE, Odlaug BL, Chamberlain SR, Keuthen NJ, Lochner C, Stein DJ. Skin picking disorder. Am J Psychiatry. 2012;169:1143–9.

10. Grant JE, Odlaug BL, Potenza MN. Addicted to hair pulling? How an alternate model of trichotillomania may improve treatment outcome. Harv Rev Psychiatry. 2007;15:80–5.

11. Bohne A, Keuthen NJ, Wilhelm S, Deckersbach T, Jenike MA. Prevalence of symptoms of body dysmorphic disorder and its correlates: a cross-cultural comparison. Psychosomatics. 2002;43:486–90.

12. Hayes SL, Storch EA, Berlanga L. Skin picking behaviors: an examination of the prevalence and severity in a community sample. J Anxiety Disord. 2009;23:314–9.

13. Radomsky AS, Alcolado GM, Abramowitz JS, Alonso P, Belloch A, Bouvard M, Clark DA, Coles ME, Doron G, Fernández-Álvarez H. Part 1—you can run but you can't hide: intrusive thoughts on six continents. J Obsessive Compuls Relat Disord. 2014;3:269–79.

14. Stanley MA, Borden JW, Mouton SG, Breckenridge JK. Nonclinical hair-pulling: affective correlates and comparison with clinical samples. Behav Res Ther. 1995;33:179–86.

15. Foa EB, Kozak MJ. DSM-iv field trial: obsessive-compulsive disorder. Am J Psychiatry. 1995;152:90.

16. Phillips KA, Pinto A, Hart AS, Coles ME, Eisen JL, Menard W, Rasmussen SA. A comparison of insight in body dysmorphic disorder and obsessive–compulsive disorder. J Psychiatr Res. 2012;46:1293–9.

17. Sookman D, Abramowitz JS, Calamari JE, Wilhelm S, McKay D. Subtypes of obsessive-compulsive disorder: implications for specialized cognitive behavior therapy. Behav Ther. 2005;36:393–400.

18. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005;62:593.

19. Weissman MM. Cross-national epidemiology of obsessive-compulsive disorder. CNS Spectr. 1998;3:6–9.

20. Angst J, Gamma A, Endrass J, Goodwin R, Ajdacic V, Eich D, Rössler W. Obsessive-compulsive severity spectrum in the community: prevalence, comorbidity, and course. Eur Arch Psychiatry Clin Neurosci. 2004;254:156–64.

21. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. Mol Psychiatry. 2010;15:53–63.

22. Zohar AH. The epidemiology of obsessive-compulsive disorder in children and adolescents. Child Adolesc Psychiatr Clin. 1999;8:445–60.

23. Abramowitz JS, Schwartz SA, Moore KM, Luenzmann KR. Obsessive-compulsive symptoms in pregnancy and the puerperium: a review of the literature. Anxiety Disord. 2003;17:18.

24. Steketee GS, Eisen J, Dyck I, Warshaw M, Rasmussen S. Predictors of course in obsessive compulsive disorder. Psychiatry Res. 1999;89:229–38.

25. García-Soriano G, Rufer M, Delsignore A, Weidt S. Factors associated with non-treatment or delayed treatment seeking in OCD sufferers: a review of the literature – science direct. Psychiatry Res. 2019;220:1–10.

26. Skoog G, Skoog I. A 40-year follow-up of patients with obsessive-compulsive disorder. Arch Gen Psychiatry. 1999;56:121–7.

27. Phillips KA, Wilhelm S, Koran LM, Didie ER, Fallon BA, Feusner J, Stein DJ. Body dysmorphic disorder: some key issues for DSM-V. Depress Anxiety. 2010;27:573–91.

28. Pope HG, Gruber AJ, Choi P, Olivardia R, Phillips KA. Muscle dysmorphia: an underrecognized form of body dysmorphic disorder. Psychosomatics. 1997;38:548–57.

29. Buhlmann U, Glaesmer H, Mewes R, Fama JM, Wilhelm S, Brähler E, Rief W. Updates on the prevalence of body dysmorphic disorder: a population-based survey. Psychiatry Res. 2010;178:171–5.

30. Conrado LA, Hounie AG, Diniz JB, Fossaluza V, Torres AR, Miguel EC, Rivitti EA. Body dysmorphic disorder among dermatologic patients: prevalence and clinical features. J Am Acad Dermatol. 2010;63:235–43.

31. Phillips KA, Menard W, Fay C, Weisberg R. Demographic characteristics, phenomenology, comorbidity, and family history in 200 individuals with body dysmorphic disorder. Psychosomatics. 2005;46:317–25.
32. Weingarden H, Curley EE, Renshaw KD, Wilhelm S. Patient-identified events implicated in the development of body dysmorphic disorder. Body Image. 2017;21:19–25.
33. Phillips KA, Menard W, Fay C. Gender similarities and differences in 200 individuals with body dysmorphic disorder. Compr Psychiatry. 2006;47:77–87.
34. Frost RO, Kim H-J, Morris C, Bloss C, Murray-Close M, Steketee GS. Hoarding, compulsive buying and reasons for saving. Behav Res Ther. 1998;36:657–64.
35. Frost RO, Steketee GS, Williams L. Hoarding: a community health problem. Health Soc Care Community. 2000;8:229–34.
36. Frost RO, Tolin DF, Steketee G, Fitch KE, Selbo-Bruns A. Excessive acquisition in hoarding. J Anxiety Disord. 2009;23:632–9.
37. Frost RO, Steketee G, Grisham J. Measurement of compulsive hoarding: saving inventory-revised. Behav Res Ther. 2004;42:1163–82.
38. Mueller A, Mueller U, Albert P, Mertens C, Silbermann A, Mitchell JE, De Zwaan M. Hoarding in a compulsive buying sample. Behav Res Ther. 2007;45:2754–63.
39. Pertusa A, Frost RO, Fullana MA, Samuels J, Steketee GS, Tolin D, Saxena S, Leckman JF, Mataix-Cols D. Refining the diagnostic boundaries of compulsive hoarding: a critical review. Clin Psychol Rev. 2010;30:371–86.
40. Ayers CR, Saxena S, Golshan S, Wetherell JL. Age at onset and clinical features of late life compulsive hoarding. Int J Geriatr Psychiatry. 2010;25:142–9.
41. Demet MM, Deveci A, Taşkın EO, Dündar PE, Ermertcan AT, Demet SM, Bayraktar D, Öztürkcan S. Risk factors for delaying treatment seeking in obsessive-compulsive disorder. Compr Psychiatry. 2010;51:480–5.
42. Frost RO, Steketee GS. Hoarding: clinical aspects and treatment strategies. Obs Compuls Disord Pract Manag. 1998:533–54. https://www.researchgate.net/profile/Gail_Steketee/publication/265121706_Chapter_23_HOARDING_CLINICAL_ASPECTS_AND_TREATMENT_STRATEGIES/links/5576cdf308aeacff1fff0f3e/Chapter-23-HOARDING-CLINICAL-ASPECTS-AND-TREATMENT-STRATEGIES.pdf
43. Lochner C, Seedat S, du Toit PL, Nel DG, Niehaus DJH, Sandler R, Stein DJ. Obsessive-compulsive disorder and trichotillomania: a phenomenological comparison. BMC Psychiatry. 2005;5:2.
44. Stein DJ, Grant JE, Franklin ME, Keuthen N, Lochner C, Singer HS, Woods DW. Trichotillomania (hair pulling disorder), skin picking disorder, and stereotypic movement disorder: toward DSM-V. Depress Anxiety. 2010;27:611–26.
45. Swedo SE. Trichotillomania. Psychiatr Ann. 1993;23:402–7.
46. Hautmann G, Hercogova J, Lotti T. Trichotillomania. J Am Acad Dermatol. 2002;46:807–26.
47. Diefenbach GJ, Tolin DF, Hannan S, Crocetto J, Worhunsky P. Trichotillomania: impact on psychosocial functioning and quality of life. Behav Res Ther. 2005;43:869–84.
48. Keuthen NJ, Koran LM, Aboujaoude E, Large MD, Serpe RT. The prevalence of pathologic skin picking in us adults. Compr Psychiatry. 2010;51:183–6.
49. Flessner CA, Woods DW. Phenomenological characteristics, social problems, and the economic impact associated with chronic skin picking. Behav Modif. 2006;30:944–63.
50. Vythilingum B, Stein DJ. Obsessive-compulsive disorders and dermatologic disease. Dermatol Clin. 2005;23:675–80.
51. Odlaug BL, Grant JE. Clinical characteristics and medical complications of pathologic skin picking. Gen Hosp Psychiatry. 2008;30:61–6.
52. Barlow DH. Anxiety and its disorders: the nature and treatment of anxiety and panic. New York: Guilford Publications; 2002.
53. Hofmann SG, Smits JAJ. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry. 2008;69:621.

54. Beck AT. Cognitive therapy and the emotional disorders. Oxford: International Universities Press; 1976.
55. Beck AT, Clark DA. An information processing model of anxiety: automatic and strategic processes. Behav Res Ther. 1997;35:49–58.
56. Rachman S. A cognitive theory of obsessions: elaborations. Behav Res Ther. 1998;36:385–401.
57. Rachman S, de Silva P. Abnormal and normal obsessions. Behav Res Ther. 1978;16:233–48.
58. Veale D. Advances in a cognitive behavioural model of body dysmorphic disorder. Body Image. 2004;1:113–25.
59. Wilhelm S, Neziroglu F. Cognitive theory of body dysmorphic disorder. In: Frost RO, Steketee G, editors. Cognitive approaches to obsessions and compulsions. Pergamon/Oxford; 2002. p. 203–14.
60. Greenberg JL, Reuman L, Hartmann AS, Kasarskis I, Wilhelm S. Visual hot spots: an eye tracking study of attention bias in body dysmorphic disorder. J Psychiatr Res. 2014;57:125–32.
61. Rachman S, Elliott CM, Shafran R, Radomsky AS. Separating hoarding from OCD. Behav Res Ther. 2009;47:520–2.
62. Christenson GA, Mackenzie TB, Mitchell JE. Characteristics of 60 adult chronic hair pullers. Am J Psychiatry. 1991;148:365.
63. Grant JE, Potenza MN. Compulsive aspects of impulse-control disorders. Psychiatr Clin North Am. 2006;29:539–51, x.
64. Grant JE, Potenza MN. Impulse control disorders: clinical characteristics and pharmacological management. Ann Clin Psychiatry. 2004;16:27–34.
65. Steketee GS, Frost RO. Compulsive hoarding and acquiring. Oxford: Oxford University Press; 2007.
66. Tolin DF, Villavicencio A, Umbach A, Kurtz MM. Neuropsychological functioning in hoarding disorder. Psychiatry Res. 2011;189:413–8.
67. Grisham JR, Brown TA, Savage CR, Steketee G, Barlow DH. Neuropsychological impairment associated with compulsive hoarding. Behav Res Ther. 2007;45:1471–83.
68. Mansueto CS, Townsley Stemberger RM, Thomas AM, Golomb RG. Trichotillomania: a comprehensive behavioral model. Clin Psychol Rev. 1997;17:567–77.
69. Franklin ME, Tolin DF. Treating trichotillomania: cognitive-behavioral therapy for hairpulling and related problems. New York: Springer Science & Business Media; 2007.
70. Abramowitz JS. The psychological treatment of obsessive-compulsive disorder. Can J Psychiatry. 2006;51(7):407–16.
71. Odlaug BL, Grant JE. Pathologic skin picking. Am J Drug Alcohol Abuse. 2010;36:296–303.
72. Phillips KA, Didie ER, Feusner J, Wilhelm S. Body dysmorphic disorder: treating an under-recognized disorder. Am J Psychiatry. 2008;165:1111–8.
73. Weingarden H, Renshaw KD. Shame in the obsessive compulsive related disorders: a conceptual review. J Affect Disord. 2015;171:74–84.
74. Abramowitz JS, Lackey GR, Wheaton MG. Obsessive–compulsive symptoms: the contribution of obsessional beliefs and experiential avoidance. J Anxiety Disord. 2009;23:160–6.
75. Fernández de la Cruz L, Landau D, Iervolino AC, Santo S, Pertusa A, Singh S, Mataix-Cols D. Experiential avoidance and emotion regulation difficulties in hoarding disorder. J Anxiety Disord. 2013;27:204–9.
76. Lebowitz ER, Panza KE, Bloch MH. Family accommodation in obsessive-compulsive and anxiety disorders: a five-year update. Expert Rev Neurother. 2016;16:45–53.
77. Abramowitz JS, Baucom DH, Wheaton MG, Boeding S, Fabricant LE, Paprocki C, Fischer MS. Enhancing exposure and response prevention for OCD: a couple-based approach. Behav Modif. 2013;37:189–210.
78. Belus JM, Baucom DH, Abramowitz JS. The effect of a couple-based treatment for OCD on intimate partners. J Behav Ther Exp Psychiatry. 2014;45:484–8.
79. Brown TA, Barlow DH. Anxiety and related disorders interview schedule for dsm-5 (adis-5l)-lifetime version. Client interview schedule 5-copy set (treatments that work); 2014.
80. First MB, Williams JBW. SCID-5-cv: structured clinical interview for dsm-5 disorders: clinician version. Arlington: American Psychiatric Association Publishing; 2016.

81. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(Suppl 2):22–33; quiz 34-57.

82. Brown TA, Di Nardo PA, Lehman CL, Campbell LA. Reliability of DSM-IV anxiety and mood disorders: implications for the classification of emotional disorders. J Abnorm Psychol. 2001;110:49–58.

83. Lobbestael J, Leurgans M, Arntz A. Inter-rater reliability of the structured clinical interview for DSM-IV axis I disorders (SCID I) and axis II disorders (SCID II). Clin Psychol Psychother. 2011;18:75–9.

84. First MB, Gibbon M. The structured clinical interview for DSM-IV axis I disorders (SCID-I) and the structured clinical interview for DSM-IV axis II disorders (SCID-II); 2004.

85. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, Janavs J, Dunbar GC. The mini international neuropsychiatric interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur psychiatry. 1997;12:224–31.

86. Sheehan DV, Lecrubier Y, Sheehan KH, Janavs J, Weiller E, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC. The validity of the mini international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry. 1997;12:232–41.

87. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. Yale-Brown obsessive compulsive scale (Y-BOCS). Arch gen psychiatry. 1989;46:1006–11.

88. Deacon BJ, Abramowitz JS. The Yale-Brown obsessive compulsive scale: factor analysis, construct validity, and suggestions for refinement. J Anxiety Disord. 2005;19:573–85.

89. Woody SR, Steketee GS, Chambless DL. Reliability and validity of the Yale-Brown obsessive-compulsive scale. Behav Res Ther. 1995;33:597–605.

90. Phillips KA, Hart AS, Menard W. Psychometric evaluation of the Yale–Brown obsessive-compulsive scale modified for body dysmorphic disorder (BDD-YBOCS). J Obsessive Compuls Relat Disord. 2014;3:205–8.

91. Stanley MA, Breckenridge JK, Snyder AG, Novy DM. Clinician-rated measures of hair pulling: a preliminary psychometric evaluation. J Psychopathol Behav Assess. 1999;21:157–70.

92. Bloch MR, Elliott M, Thompson H, Koran LM. Fluoxetine in pathologic skin-picking: open-label and double-blind results. Psychosomatics. 2001;42:314–9.

93. Tolin DF, Frost RO, Steketee GS. A brief interview for assessing compulsive hoarding: the hoarding rating scale-interview. Psychiatry Res. 2010;178:147–52.

94. Tolin DF, Gilliam CM, Davis E, Springer K, Levy HC, Frost RO, Steketee GS, Stevens MC. Psychometric properties of the hoarding rating scale-interview. J Obsessive Compuls Relat Disord. 2018;16:76–80.

95. Swedo SE, Leonard HL, Rapoport JL, Lenane MC, Goldberger EL, Cheslow DL. A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). N Engl J Med. 1989;321:497–501.

96. Ninan PT, Rothbaum BO, Marsteller FA, Knight BT, Eccard MB. A placebo-controlled trial of cognitive-behavioral therapy and clomipramine in trichotillomania. J Clin Psychiatry. 2000;61:47–50.

97. Norman SB, Campbell-Sills L, Hitchcock CA, Sullivan S, Rochlin A, Wilkins KC, Stein MB. Psychometrics of a brief measure of anxiety to detect severity and impairment: the overall anxiety severity and impairment scale (oasis). J Psychiatr Res. 2011;45:262–8.

98. Abramowitz JS, Deacon BJ, Olatunji BO, et al. Assessment of obsessive-compulsive symptom dimensions: development and evaluation of the dimensional obsessive-compulsive scale. Psychol Assess. 2010;22:180–98.

99. Wilhelm S, Greenberg JL, Rosenfield E, Kasarskis I, Blashill AJ. The body dysmorphic disorder symptom scale: development and preliminary validation of a self-report scale of symptom specific dysfunction. Body Image. 2016;17:82–7.

100. Fang A, Sawyer AT, Aderka IM, Hofmann SG. Psychological treatment of social anxiety disorder improves body dysmorphic concerns. J Anxiety Disord. 2013;27:684–91.

101. Greenberg JL, Mothi SS, Wilhelm S. Cognitive-behavioral therapy for adolescent body dysmorphic disorder: a pilot study. Behav Ther. 2016;47:213–24.
102. Wilhelm S, Phillips KA, Didie E, Buhlmann U, Greenberg JL, Fama JM, Steketee GS. Modular cognitive-behavioral therapy for body dysmorphic disorder: a randomized controlled trial. Behav Ther. 2014;45:314–27.
103. Mohammadzadeh A. Validation of saving inventory-revised (SI-R): compulsive hoarding measure. Iran J Psychiatry Clin Psychol. 2009;15:33–41.
104. Keuthen NJ, Wilhelm S, Deckersbach T, Engelhard IM, Forker AE, Baer L, Jenike MA. The skin picking scale: scale construction and psychometric analyses. J Psychosom Res. 2001;50:337–41.
105. Keuthen NJ, Deckersbach T, Wilhelm S, Engelhard I, Forker A, O'sullivan RL, Jenike MA, Baer L. The skin picking impact scale (SPIS): scale development and psychometric analyses. Psychosomatics. 2001;42:397–403.
106. Tucker BTP, Woods DW, Flessner CA, Franklin SA, Franklin ME. The skin picking impact project: phenomenology, interference, and treatment utilization of pathological skin picking in a population-based sample. J Anxiety Disord. 2011;25:88–95.
107. Keuthen NJ, O'Sullivan RL, Ricciardi JN, Shera D, Savage CR, Borgmann AS, Jenike MA, Baer L. The Massachusetts General Hospital (MGH) hairpulling scale: 1. Development and factor analyses. Psychother Psychosom. 1995;64:141–5.
108. Keuthen NJ, Flessner CA, Woods DW, Franklin ME, Stein DJ, Cashin SE. Factor analysis of the Massachusetts General Hospital hairpulling scale. J Psychosom Res. 2007;62:707–9.
109. O'Sullivan RL, Keuthen NJ, Hayday CF, Ricciardi JN, Buttolph L, Jenike MA, Baer L. The Massachusetts General Hospital (MGH) hairpulling scale: 2. Reliability and validity. Psychother Psychosom. 1995;64:146–8.
110. Diefenbach GJ, Tolin DF, Hannan S, Maltby N, Crocetto J. Group treatment for trichotillomania: behavior therapy versus supportive therapy. Behav Ther. 2006;37:353–63.
111. Grant JE, Odlaug BL, Kim SW. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. Arch Gen Psychiatry. 2009;66:756–63.
112. Phillips KA, Pinto A, Menard W, Eisen JL, Mancebo M, Rasmussen SA. Obsessive–compulsive disorder versus body dysmorphic disorder: a comparison study of two possibly related disorders. Depress Anxiety. 2007;24:399–409.
113. Wilhelm S, Phillips KA, Steketee G. Cognitive-behavioral therapy for body dysmorphic disorder: a treatment manual. New York/London: Guilford Press; 2012.
114. Rasmussen SA, Eisen JL. The epidemiology and differential diagnosis of obsessive compulsive disorder. The Journal of clinical psychiatry. 1994;55:5–10.
115. Langlois F, Freeston MH, Ladouceur R. Differences and similarities between obsessive intrusive thoughts and worry in a non-clinical population: study 1. Behav Res Ther. 2000;38:157–73.
116. McEvoy PM, Watson H, Watkins ER, Nathan P. The relationship between worry, rumination, and comorbidity: evidence for repetitive negative thinking as a transdiagnostic construct. J Affect Disord. 2013;151:313–20.
117. Norr AM, Oglesby ME, Capron DW, Raines AM, Korte KJ, Schmidt NB. Evaluating the unique contribution of intolerance of uncertainty relative to other cognitive vulnerability factors in anxiety psychopathology. J Affect Disord. 2013;151:136–42.
118. Fang A, Hofmann SG. Relationship between social anxiety disorder and body dysmorphic disorder. Clin Psychol Rev. 2010;30:1040–8.
119. Dykshoorn KL. Trauma-related obsessive-compulsive disorder: a review. Health Psychol Behav Med. 2014;2:517–28.
120. Fontenelle LF, Cocchi L, Harrison BJ, et al. Towards a post-traumatic subtype of obsessive–compulsive disorder. J Anxiety Disord. 2012;26:377–83.
121. de Araújo AXG, Fontenelle LF, Berger W, da Luz MP, Pagotto LFADC, Marques-Portella C, Figueira I, Mendlowicz MV. Pre-traumatic vs post-traumatic OCD in PTSD patients: are differences in comorbidity rates and functional health status related to childhood abuse? Compr Psychiatry. 2018;87:25–31.

122. Gershuny BS, Keuthen NJ, Gentes EL, Russo AR, Emmott EC, Jameson M, Dougherty DD, Loh R, Jenike MA. Current posttraumatic stress disorder and history of trauma in trichotillomania. J Clin Psychol. 2006;62:1521–9.

123. Olatunji BO, Deacon BJ, Abramowitz JS. Is hypochondriasis an anxiety disorder? Br J Psychiatry. 2009;194:481–2.

124. Abramowitz JS, Schwartz SA, Whiteside SP. A contemporary conceptual model of hypochondriasis. Mayo Clin Proc. Elsevier. 2002;77(12):1323–30.

125. Jacoby RJ, Abramowitz JS. Treatment of comorbid depression and obsessive-compulsive disorder. In: Storch EA, Lewin AB, editors. Clinical handbook of obsessive-compulsive and related disorders. A case-based approach to treating pediatric and adult populations. Cham: Springer International Publishing; 2016. p. 371–83.

126. Mancebo MC, Grant JE, Pinto A, Eisen JL, Rasmussen SA. Substance use disorders in an obsessive compulsive disorder clinical sample. J Anxiety Disord. 2009;23:429–35.

127. Fals-Stewart W, Schafer J. The treatment of substance abusers diagnosed with obsessive-compulsive disorder: an outcome study. J Subst Abuse Treat. 1992;9:365–70.

128. Hofmann SG, Asnaani A, Vonk IJJJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cogn Ther Res. 2012;36:427–40.

129. McKay D, Sookman D, Neziroglu F, Wilhelm S, Stein DJ, Kyrios M, Matthews K, Veale D. Efficacy of cognitive-behavioral therapy for obsessive–compulsive disorder. Psychiatry Res. 2015;225:236–46.

130. Abramowitz JS, Jacoby RJ. Obsessive-compulsive disorder in adults. Boston: Hogrefe Publishing; 2014.

131. Wilhelm S, Steketee GS. Cognitive therapy for obsessive compulsive disorder: a guide for professionals. Oakland: New Harbinger Publications; 2006.

132. Obsessive Compulsive Cognitions Working Group. Psychometric validation of the obsessive belief questionnaire and interpretation of intrusions inventory—part 2: factor analyses and testing of a brief version. Behav Res Ther. 2005;43:1527–42.

133. Olatunji BO, Davis ML, Powers MB, Smits JAJJ. Cognitive-behavioral therapy for obsessive-compulsive disorder: a meta-analysis of treatment outcome and moderators. J Psychiatr Res. 2013;47:33–41.

134. Olatunji BO, Rosenfield D, Tart CD, Cottraux J, Powers MB, Smits JAJ. Behavioral versus cognitive treatment of obsessive-compulsive disorder: an examination of outcome and mediators of change. J Consult Clin Psychol. 2013;81:415.

135. Saxena S, Maidment KM. Treatment of compulsive hoarding. J Clin Psychol. 2004;60:1143–54.

136. Steketee GS, Frost RO. Treatment for hoarding disorder: therapist guide. 2nd ed. New York: Oxford University Press; 2014.

137. PÉLissier M-C, O'Connor K. Cognitive-behavioral treatment of trichotillomania, targeting perfectionism. Clin Case Stud. 2004;3:57–69.

138. Foa EB, Yadin E, Lichner TK. Exposure and response (ritual) prevention for obsessive compulsive disorder: therapist guide. Oxford: Oxford University Press; 2012.

139. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behav Res Ther. 2008;46:5–27.

140. Arch JJ, Abramowitz JS. Exposure therapy for obsessive–compulsive disorder: an optimizing inhibitory learning approach. J Obsessive Compuls Relat Disord. 2015;6:174–82.

141. Foa EB, Kozak MJ. Emotional processing of fear: exposure to corrective information. Psychol Bull. 1986;99:20.

142. Bloch MH, Landeros-Weisenberger A, Dombrowski P, Kelmendi B, Wegner R, Nudel J, Pittenger C, Leckman JF, Coric V. Systematic review: pharmacological and behavioral treatment for trichotillomania. Biol Psychiatry. 2007;62:839–46.

143. Lochner C, Roos A, Stein DJ. Excoriation (skin-picking) disorder: a systematic review of treatment options. Neuropsychiatr Dis Treat. 2017;13:1867.

144. Azrin NH, Nunn RG. Habit-reversal: a method of eliminating nervous habits and tics. Behav Res Ther. 1973;11:619–28.

145. Morris SH, Zickgraf HF, Dingfelder HE, Franklin ME. Habit reversal training in trichotillomania: guide for the clinician. Expert Rev Neurother. 2013;13:1069–77.

146. Falkenstein MJ, Mouton-Odum S, Mansueto CS, Golomb RG, Haaga DAF. Comprehensive behavioral treatment of trichotillomania: a treatment development study. Behav Modif. 2016;40:414–38.

147. Himle JA, Bybee D, O'Donnell LA, Weaver A, Vlnka S, DeSena DT, Rimer JM. Awareness enhancing and monitoring device plus habit reversal in the treatment of trichotillomania: an open feasibility trial. J Obsessive Compuls Relat Disord. 2018;16:14–20.

148. Barlow DH, Farchione TJ, Sauer-Zavala S, Latin HM, Ellard KK, Bullis JR, Bentley KH, Boettcher HT, Cassiello-Robbins C. Unified protocol for transdiagnostic treatment of emotional disorders: therapist guide. Oxford: Oxford University Press; 2017.

149. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. Behav Res Ther. 2006;44:1–25.

150. Ellard KK, Fairholme CP, Boisseau CL, Farchione TJ, Barlow DH. Unified protocol for the transdiagnostic treatment of emotional disorders: protocol development and initial outcome data. Cogn Behav Pract. 2010;17:88–101.

151. Barlow DH, Farchione TJ, Bullis JR, et al. The unified protocol for transdiagnostic treatment of emotional disorders compared with diagnosis-specific protocols for anxiety disorders. JAMA PsychiatJAMA Psychiatry. 2017;74:875.

152. Farchione TJ, Fairholme CP, Ellard KK, Boisseau CL, Thompson-Hollands J, Carl JR, Gallagher MW, Barlow DH. Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. Behav Ther. 2012;43:666–78.

153. Bluett EJ, Homan KJ, Morrison KL, Levin ME, Twohig MP. Acceptance and commitment therapy for anxiety and OCD spectrum disorders: an empirical review. J Anxiety Disord. 2014;28:612–24.

154. Twohig MP, Abramowitz JS, Bluett EJ, Fabricant LE, Jacoby RJ, Morrison KL, Reuman L, Smith BM. Exposure therapy for OCD from an acceptance and commitment therapy (act) framework. J Obsessive Compuls Relat Disord. 2015;6:167–73.

155. Follette V, Heffner M, Pearson A. Acceptance and commitment therapy for body image dissatisfaction: a practitioner's guide to using mindfulness, acceptance, and values-based behavior change strategies. Oakland: New Harbinger Publications; 2010.

156. Twohig MP, Hayes SC, Masuda A. A preliminary investigation of acceptance and commitment therapy as a treatment for chronic skin picking. Behav Res Ther. 2006;44:1513–22.

157. Lee EB, Homan KJ, Morrison KL, Ong CW, Levin ME, Twohig MP. Acceptance and commitment therapy for trichotillomania: a randomized controlled trial of adults and adolescents. Behav Modif. 2018; https://doi.org/10.1177/0145445518794366.

158. Twohig MP, Hayes SC, Masuda A. Increasing willingness to experience obsessions: acceptance and commitment therapy as a treatment for obsessive-compulsive disorder. Behav Ther. 2006;37:3–13.

159. Twohig MP, Hayes SC, Plumb JC, Pruitt LD, Collins AB, Hazlett-Stevens H, Woidneck MR. A randomized clinical trial of acceptance and commitment therapy versus progressive relaxation training for obsessive-compulsive disorder. J Consult Clin Psychol. 2010;78:705–16.

160. Twohig MP, Abramowitz JS, Smith BM, Fabricant LE, Jacoby RJ, Morrison KL, Bluett EJ, Reuman L, Blakey SM, Lederman T. Adding acceptance and commitment therapy to exposure and response prevention for obsessive-compulsive disorder: a randomized controlled trial. Behav Res Ther. 2018 108:1-9.

161. Juarascio AS, Forman EM, Herbert JD. Acceptance and commitment therapy versus cognitive therapy for the treatment of comorbid eating pathology. Behav Modif. 2010;34:175–90.

162. Pearson AN, Follette VM, Hayes SC. A pilot study of acceptance and commitment therapy as a workshop intervention for body dissatisfaction and disordered eating attitudes. Cogn Behav Pract. 2012;19:181–97.

163. Teng EJ, Woods DW, Twohig MP. Habit reversal as a treatment for chronic skin picking: a pilot investigation. Behav Modif. 2006;30:411–22.

Chapter 7
Anxiety Disorders in Children

Sophie A. Palitz and Philip C. Kendall

Introduction and Overview

Anxiety is a normal emotion that all youth experience: indeed, anxiety is necessary for survival [1]. However, anxiety can grow to a point where it becomes maladaptive, interfering and associated with unwanted functional difficulties. Anxiety disorders are one of the most common class of disorders seen in childhood and adolescence [2, 3], with prevalence rates estimated to be between 10% and 32% [3, 4]. Anxiety disorders in youth are associated with a myriad of other problems, including poorer educational achievement [5], impairments in psychosocial functioning [6], and increased rates of suicidal ideation [7–9]. Moreover, if left untreated, the anxiety disorders are likely to persist into adulthood [4, 10]. Although effective treatments for anxiety exist, additional work is needed to continue to improve outcomes for youth who struggle with anxiety disorders.

In the sections that follow, we will first discuss the common ways in which anxiety disorders present in children and adolescents. We will then address treatments for these disorders, followed by a discussion of developmental considerations in youth anxiety. The chapter concludes with directions for future research.

Symptom Presentation of Common Youth Anxiety Disorders

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [11] recognizes several anxiety disorder diagnoses seen in childhood and adolescence. These include separation anxiety disorder (SepAD), generalized anxiety disorder (GAD), social anxiety disorder (SocAD), selective mutism (SM), specific

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phobias (SP), panic disorder (PD), and agoraphobia. The most common of these disorders are SepAD, GAD, SocAD, SM, and SP, which are thus discussed in more detail below. Although the decision is not universally accepted, DSM-5 no longer classifies obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) as anxiety disorders.

Specific phobia is the most common anxiety disorder in youth [3] and is marked by meaningful and disproportionate fear when the youth encounters a specific object or situation. Common categories of SPs include animals/insects (e.g., bees, dogs), darkness, and blood-injection-injury type (e.g., needles, shots) [11]. In SP, the specific object or situation almost always is associated with marked fear and results in avoidance or extreme distress if it cannot be avoided [11]. For example, if a child is afraid of spiders and requests a parent to come kill spiders when present in the house, this fear does not necessarily warrant a diagnosis of SP as it is not necessarily resulting in avoidance or extreme distress. If, however, this child refuses to go back into the room in the house where there was a spider a few days ago even if it has been killed, or if he or she is excessively distressed by a family hike – crying hysterically and experiencing an elevated heart rate – as there may be a spider in the woods along the hike, this avoidance and distress (respectively) indicate a clinical diagnosis may be warranted.

Youth with social anxiety disorder experience anxiety surrounding how they will be perceived by others in social situations. They often avoid social situations or endure them with great distress due to concerns that they will be rejected or laughed at by others. As some anxiety in social situations is normative, to meet diagnostic criteria for SocAD, a youth must almost always experience persistent anxiety in a variety of social situations and experience symptoms [11]. Additionally, the youth's fear must be out of proportion to the threat posed by the social situation, must produce prolonged functioning impairment and distress, and must be associated with physical symptoms in the anxiety-provoking social situations such as freezing, hiding, or crying [11]. SocAD may present for youth in various ways, such as difficulty asking questions in class, starting or joining conversations, ordering for oneself at a restaurant, or eating in front of others. Additionally, it may result in a youth withdrawing from extracurricular activities and social events such as birthday parties or school activity nights. Of note, for a child or adolescent to receive a diagnosis of SocAD, the anxiety must be present in social situations with peers and cannot be confined to interactions solely with adults [11].

Youth with separation anxiety disorder experience excessive and developmentally inappropriate anxiety when separating from a parent or other attachment figures [11]. This diagnosis is not given to children under the age of six as trouble separating from attachment figures is seen as developmentally normative until this point. Youth with SepAD often experience difficulty separating from parents (or other attachment figures), worry about potential harm to oneself or one's parents when separated, avoidance of being alone, and/or refusal to go to certain places without one's parents [11]. They may also experience nightmares with a separation theme, have trouble going to sleep alone or in their own room, refuse to go to school due to distress surrounding separation, or wish to contact their caregiver (e.g., with frequent calls or texts) when the caregiver is not there. SepAD may be accompanied by physical symptoms of anxi-

ety when the youth experiences separation or when separation is anticipated [11]. It is important to note that parents may serve as safety figures for youth with other anxiety disorders besides SepAD, such that these youth are comforted when their parents are around and thus may cling to their parents, even if they do not have SepAD. For example, a youth with SocAD (discussed above) may cling to a parent in social situations as the parent may speak for the child, even though the child does not have SepAD and is not worried about separating when not in a social situation.

Generalized anxiety disorder in youth, as in adults, is associated with excessive and persistent worry about various topics including academics, changes in plans, perfectionism, performing up to a high standard, local or world affairs, and the future [11]. To receive a diagnosis of GAD, youth must have persistent symptoms that occur more days than not, experience the worry as difficult to control, and have at least one associated physical or behavioral symptom such as muscle tensions, irritability, or excessive reassurance seeking behaviors [11]. Children and adolescents with GAD may engage in other related behaviors such as avoiding doing something that may not work out how they want it to, redoing work to perfection, and procrastinating due to anxiety about the task [11]. As worry may be appropriate or reasonable at times and in some situations, it is often compared to that of the youth's peers to assess if it is excessive and inappropriate.

Selective mutism is characterized by a failure to speak in certain, specific social situations not attributable to a lack of knowledge or comfort with the spoken language [11]. That is, while these youth possess the ability to speak and do so in some situations (e.g., at home), they refuse to do so in other specific situations, such as at school, with friends, or with relatives they do not know well. To meet diagnostic criteria, a youth must experience functional interference due to the refusal to speak in specific situations [11]. SM is typically comorbid with SocAD.

Youth with anxiety disorders often have multiple mental health diagnoses, with comorbid diagnoses being the norm in community settings [12], although this is not fully represented in research settings where inclusion/exclusion criteria may preclude this. The most common comorbid diagnosis in anxious youth is another anxiety disorder; indeed, roughly 80% of youth with anxiety meet diagnostic criteria for multiple anxiety disorders [13]. The prevalence of comorbidity highlights the importance of tailoring treatment to the individual youth. Of course, it warrants acknowledgment that the high rates of comorbidity may be somewhat a function of the categorical diagnostic system of the DSM-5, and a more continuous approach to diagnoses may provide a different understanding of comorbidities. Nonetheless, it remains important to consider comorbidities when treating anxious youth.

Treatment

Anxiety disorders are highly prevalent among children and adolescents [3, 4], and effective treatments have been identified through extensive research [14]. Studies support cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibi-

tors (SSRIs) as effective for treating anxiety in children and adolescents [15–17]. In the following sections, we will elaborate on these two interventions, followed by a brief discussion of other approaches that have been studied.

Cognitive Behavioral Therapy (CBT)

CBT is considered, using the criteria of the Division of Clinical Psychology of the American Psychological Association, to be a "well-established" intervention for treating children and adolescents with anxiety [18]. CBT has received much research attention since the initial CBT treatment for child anxiety, the *Coping Cat* program [19, 20], was developed and received empirical support [21]. Since that time, the specific treatment protocol has been adapted for use with adolescents (the *C.A.T. Project*) [22] and for use in different countries and languages (e.g., in Norway) [23]. Related adaptations of the protocol have been developed (e.g., Cool Kids) [24], which have similarly demonstrated their efficacy in treating children and adolescents with anxiety [14, 25]. In the largest study to date that has investigated youth anxiety treatment – the Child/Adolescent Anxiety Multimodal Study (CAMS) [17] – 60% of the youth who received CBT (specifically the *Coping Cat* and *C.A.T. Project* protocols) were rated as "very much improved" or "much improved" by an independent evaluator following treatment. This outcome was a significantly larger percentage than those who had received pill placebo and was comparable to that for those who had received medication (see below for a discussion on medication to treat youth anxiety). Indeed, CBT for youth anxiety consistently outperforms waitlist conditions [26], as well as inactive and active comparison conditions [27, 28].

   CBT involves many components, designed to address the physiological, cognitive, and behavioral features of anxiety. While there are many CBT protocols for youth anxiety, all tend to include similar elements; typically, CBT involves psycho-education, relaxation training, cognitive restructuring, problem solving, and exposure to anxiety-provoking situations. Of note, research indicates that exposure to anxiety-provoking situations is a vital component of CBT for youth anxiety [29, 30] and should not be omitted. The first phase of treatment typically involves assisting the youth in learning coping strategies that include recognizing when they are anxious and then knowing what to do about it [31]. This is followed by the second phase of treatment – the exposures, often referred to as "challenges" with youth – in which the youth apply the skills they have learned in the first part of treatment as they enter anxiety-provoking situations that increase in difficulty. In this way, youth approach the situations that they previously avoided, learning they are able to handle those situations. During this phase of treatment, youth additionally complete similar exposure tasks between sessions as homework [31], often called by a different name to eschew the negative connotations many youth have with the term "homework." These out-of-session tasks reinforce what the youth have learned in session and encourage generalization of this learning to the real situations that come up in their lives.

The *Coping Cat* program is one of the most (if not *the* most) widely used protocols for youth anxiety treatment and follows this general structure of two phases with the inclusion of homework tasks. As an example of what CBT for youth anxiety looks like, we provide a brief summary of the sessions of this treatment. Throughout this treatment, the therapist works with the child to build a fear hierarchy, which can be modified as therapy progresses. Additionally throughout the treatment, the therapist assigns Show That I Can (STIC) tasks (i.e., homework) for the youth to practice what has been taught in session. Overall, the program is 16 sessions, which ideally corresponds with 16 weeks.

The initial session is focused heavily on rapport building and orienting the child to the treatment; as youth are often not self-referred and/or may be anxious about the treatment in general, rapport building early on is very important. The second and third sessions focus on building emotional awareness, with the second session discussing physical expressions of a variety of emotions including anxiety, and the third session focused on the child's own specific somatic reactions to anxiety. In the third session, the therapist also introduces the four-step plan, known as the FEAR plan, to help youth learn to cope with anxiety. In introducing the FEAR plan in session 3, the therapist teaches the youth the F step: *F*eeling frightened, which is about the child identifying how he or she is feeling, identifying the bodily cues, and recognizing the level of anxiety he or she is feeling. The fourth session is the first of the two parent sessions, during which the therapist provides the parents with more information on treatment and how they can be involved, discusses their concerns, and learns more about situations in which the child becomes anxious.

The following psychoeducation sessions are focused on skill building. Session 5 is centered on relaxation training, followed by cognitive restructuring in session 6. Session 6 is also when the child learns the E step of the FEAR plan: *E*xpecting bad things to happen, which is about recognizing the anxious automatic thoughts. In session 7, the client learns problem solving as well as the A step of the FEAR plan: *A*ttitudes and actions that can help, which helps the child remember to use the tools he or she has learned in the skill building phase to approach the anxiety-provoking situation. In the eighth session, the youth learns about making self-evaluations and rewarding oneself even if he/she does not do a perfect job. Additionally, the youth learns the final step of the FEAR plan, the R step: *R*esults and *R*ewards. This step is focused on applying self-evaluation and recognizing the rewards of doing something anxiety-provoking. As this is the final session the child has with the therapist before beginning exposures, the therapist reviews the complete FEAR plan with the child, continues work on building the youth's fear hierarchy, and identifies rewards the child might want to earn for completing challenges (i.e., exposures). The ninth session is the second parent session, during which the therapist prepares the parents for the beginning of exposure tasks in the following session, discusses their role in these exposures and in conducting them at home, and discusses any additions they may have to the fear hierarchy.

Session 10 marks the beginning of the exposure phase in treatment. During this phase of treatment, the STIC tasks assigned are the "challenges" to be completed out of session. In each exposure session (session 10 through session 16), the thera-

pist and client go through the FEAR plan to prepare for the challenge, complete the challenge, and then process how the challenge went. The challenges in sessions 10 and 11 are low anxiety-provoking situations, those in sessions 12 and 13 are moderately anxiety-provoking situations, and those in sessions 14, 15, and 16 are high anxiety-provoking situations. As the treatment program is 16 sessions, in sessions 15 and 16, the therapist discusses the end of treatment, including relapse prevention, with the youth and family. Additionally in session 16, the youth creates a "commercial" of some sort to demonstrate what they have learned in treatment, and the therapist and client (as well as sometimes the client's family) celebrate the child's success. This conclusion of treatment recognizes the child's accomplishments and encourages them to continue to approach situations so they can continue to overcome fears that arise.

Well-researched and evaluated treatment manuals such as this *Coping Cat* program exist and are used by many clinicians when treating anxious youth. As illustrated above with the *Coping Cat* program, these provide frameworks by which clinicians can deliver evidence-based therapy to children and adolescents with anxiety disorders. When working with these manuals, it remains essential for clinicians to implement them in a flexible way to meet the youth's needs while remaining adherent to the treatment; indeed the principle of "flexibility within fidelity" has been noted to be of great importance when implementing manualized treatment [32, 33]. Through this approach, the effectiveness of manualized CBT in clinical community centers has been found to be comparable to that in specialty clinics [34].

The majority of the research on CBT has focused on its use with youth ages 7–17; however preliminary research indicates it may be effective for children as young as age 4 [35, 36]. The original format of CBT – individual, youth-focused treatment – has also been modified in various ways that have similarly received empirical support, although they have been studied less often. For instance, CBT has demonstrated efficacy in the group format [34, 37–41] as well as family format, which involves both the youth and the parent or parents in every session [42, 43]. It has also demonstrated efficacy in a brief format [44] or even in as few as one extended session when treating specific phobias [45]. Modifications of the treatment to take a more transdiagnostic approach and address the anxiety within the larger context of the youth's presentation (e.g., comorbid non-anxiety disorders) have additionally demonstrated efficacy for treating anxiety in youth [46, 47]. Research has also evaluated the beneficial role technology may play in treating anxious youth. Findings indicate that computer-assisted CBT (in which some of the treatment is carried out independently via a computer CBT program and some of the treatment is completed with the assistance of a therapist) as well as internet-based CBT programs (in which all sessions are completed online and youth have two brief phone calls with a therapist) yield positive treatment outcomes for anxious youth [48–51]. Thus although the original format of CBT remains the most common when treating youth with anxiety, additional possibilities exist and possess their own benefits.

Selective Serotonin Reuptake Inhibitors (SSRIs)

CBT is considered the "gold standard" treatment for youth with anxiety, often recommended before the use of medication [52]. However, for youth who do not respond to CBT or continue to experience significant symptoms of anxiety following a course of CBT, SSRIs have been found to be beneficial [53]. Sertraline, fluvoxamine, fluvoxamine, paroxetine, and venlafaxine are among the SSRIs that have been researched and are prescribed for youth with anxiety. Multiple placebo-controlled studies have found SSRIs to be effective for treating children and adolescents with anxiety [17, 54–61], with a response rate similar to that of CBT [17]. SSRIs can be used to treat anxious youth alone or in combination with CBT. Research indicates that when youth are treated with the combination of these interventions, the response rate increases from 55% (SSRIs alone) or 60% (CBT alone) to 80% (SSRIs and CBT combined) [17]. As medication use may have unwanted costs and side effects, and the long-term effects have not been studied in youth, CBT is considered the front-line intervention for anxiety by the American Academy of Child and Adolescent Psychiatry [62], and medication can be added on following a course of CBT if that is deemed appropriate for the individual youth.

Other Interventions

Although research findings consistently support CBT and SSRIs to treat children and adolescents with anxiety, other interventions have been suggested and researched yet to a lesser extent. These include psychosocial treatments as well as additional medication. Among these additional interventions, parent programs (the therapist's intervention remains youth focused in working with the parents, teaching the parents skills to use with their children) and parent therapies (the therapist's work is not directly focused on the youth and instead centers around the parents' behaviors) have research support to suggest their efficacy in treating youth with anxiety.

For instance, *The Child Anxiety Tales* (available at CopingCatParents.com) is an example of a parent program and is based off of the *Coping Cat* treatment. This parent program has demonstrated effectiveness in making parents of children with anxiety feel empowered and more knowledgeable about anxiety in children, as well as informed about strategies that could help [63].

Parent therapies are parent focused, in contrast to CBT, which is youth focused. In these parent therapies, the therapist works with the parents to change their actions, behaviors, and ways of relating to their child so as to affect change in the youth's anxiety. Parent-Child Interaction Therapy (PCIT) is one form of parent therapy that has been well researched [64]. PCIT has been adapted from its original version, developed to treat disruptive behavior problems in children, to treat child anxiety [65]. In this therapy, the parent-child interaction is changed in order to improve the child's behavior. Following pilot studies of PCIT adapted to treat child anxiety [66,

67], an initial RCT of this adapted PCIT indicated efficacy for treating children ages 4–8 with SepAD [67]. Thus, although more research is clearly needed on this intervention, PCIT appears promising as a treatment for young children with anxiety.

Another example of parent therapy is *The SPACE Program* (Supportive Parenting for Anxious Childhood Emotions) [68]. This approach is a parent-only intervention that targets the accommodating behaviors of the parents that are related to the youth's anxiety. This treatment does not work to teach parents specific skills to implement, but rather focuses on how the parents are interacting with their child surrounding the child's anxiety and the relational features of the interactions [68]. Results from a small open trial in youth ages 9–13 provide preliminary support for the efficacy of this parenting skills training program to treat youth anxiety [68]. This approach may be valuable given that some youth may refuse individual treatment, as was the case in the sample of families who participated in this open trial [68]. As is true for PCIT, this intervention requires further investigation to assess its ability to treat youth anxiety.

There are several additional psychosocial interventions that warrant additional study in the treatment of youth anxiety. For instance, acceptance-, mindfulness-, and meditation-based interventions are established treatments for adults. With youth, the findings indicate that these approaches are acceptable and feasible [69–71], yet studies comparing these interventions to treatment-as-usual or to an active control condition have been inconsistent, with some suggesting these approaches to be better than the comparison group [72] and others finding no significant differences [73]. Overall, it has been concluded that more empirical evidence is needed to assess whether or not these treatments can be considered empirically supported [53, 69, 74, 75].

Furthermore, art therapy, music therapy, and play therapy may, in practice, be implemented to treat anxious youth; however, little research has examined these approaches' efficacy for treating anxiety disorders, and the current research does not support their efficacy [14]. The research that does presently exist has examined changes in anxiety levels from pre- to post-treatment in specialized populations, such as youth with cancer [76], youth who are going to have an operation [77], or youth who have experienced sexual assault [78]. These studies indicate that a course of art therapy or music therapy is associated with decreased self-reported anxiety symptoms [76, 78]; however of note, these studies were not of youth with anxiety disorders. One study evaluated play therapy compared to an active control condition for children with heightened levels of anxiety [79]. In this study, the play therapy group and control group were not themselves comparable, which limits the reported finding that the play therapy group reduced self-reported worry more than the control group. Moreover, the two groups were not found to be significantly different in changes in self-reported physiological anxiety or social anxiety. Thus, while these approaches of art, music, and play therapies may be employed by clinicians to address youth anxiety, the quantity and quality of the research that has been conducted on these interventions is not currently sufficient to claim empirical support.

With regard to other medications, research has examined the use of benzodiazepines to treat anxiety in children and adolescents: results have been mixed [80]. An open-label trial of 12 adolescents found that 4 weeks of alprazolam led to significant

improvements in anxiety [81], but placebo-controlled trials of alprazolam [82] and clonazepam [83] found that the benzodiazepines were no more effective than placebo. Additionally, a large majority of the participants reported frequent unwanted side effects from the medication [83]. Beyond the medical side effects, benzodiazepine use may also interfere with the benefits of psychotherapy as they have been found to interfere with new learning, a key goal of exposure tasks [84]. As a result of these inconsistent findings as well as the associated side effects, it is suggested that other interventions be implemented first and that benzodiazepines only be prescribed to youth in limited situations [85].

Special Considerations for Anxiety in Youth

Many aspects of anxiety in youth may look similar to that in adults, but there are important developmental and logistical considerations when thinking about anxiety in children and adolescents and when working with these youth. This includes developmentally informed diagnostic procedures, developmentally appropriate interventions, the role of parental accommodation in youth anxiety, and the role of parents in the treatment. As discussed above, it is necessary to consider what is developmentally appropriate when assessing anxious children and adolescents. For example, it may be developmentally appropriate for a 7-year-old to be afraid of the dark and insist on sleeping with a nightlight; however, this would no longer seem developmentally appropriate for a 17-year-old. Likewise, while it would be appropriate for a 17-year-old to have some worries associated with getting into college, the same would not be true for a 7-year-old. Developmental appropriateness is important to consider when making a diagnosis for youth.

Additionally, when implementing the treatment, there are additional considerations clinicians must consider. First, children and adolescents may not themselves be choosing to be in treatment the way an adult might be if he/she has sought the help for him/herself. Instead, youth may be brought to therapy because their parents would like them to be there. Consequently, it is especially important for therapists to spend time on building a good working relationship to increase the youth's motivation for and compliance with treatment. This effort may be especially important given that some youth may not be aware of the existence of problems when they begin therapy [86]. The outcome of treatment itself benefits when efforts are made to adapt the treatment to be age-appropriate in terms of both language and structure. For example, in a discussion of externalizing the anxiety and using cognitive restructuring, younger children may benefit from an approach that asks "What is the worry monster is saying to you?" (rather than asking them to identify negative automatic thoughts) and then having them ask themselves how they can "talk back to the worry monster" (i.e., come up with coping thoughts). In this way, youth can be taught the same challenge to unhelpful thinking as adults may learn in cognitive behavioral therapy but presented in a developmentally appropriate manner. Additionally, following a school day, many younger children may have difficulty

simply sitting and speaking with a therapist for an hour. To increase engagement, it can be beneficial to create activities with the treatment material, such as having children make a life-sized drawing of themselves and then drawing on it where they feel anxiety in their body. Older youth, on the other hand, may be able to simply discuss their physical symptoms of anxiety. The use of such strategies can make the material more interactive for the youth and help facilitate not only greater enjoyment but also greater understanding and memory of the therapeutic principles.

Another important consideration is parental and family accommodation: the ways in which a parent or the family acts to, in the moment, reduce their child's anxiety and distress [87]. Parental accommodation includes modifying their or the family's routine, providing reassurance or reducing expectations for this child. These accommodations are all seen as ways the parent or family "gives in" to the child's anxiety, and while they function to reduce anxiety temporarily, it reinforces the youth's anxiety and reinforces the avoidance over the long run. When diagnosing and treating anxious youth, it is important to recognize that the interference from the anxiety may not just be related to the child or adolescent but may instead (or in addition) be related to the parents or the family in this way. A child who has anxiety surrounding separation from a parent may not experience any interference from this anxiety if the parent has changed his or her whole schedule to enable the child to always be with him/her. This parent, on the other hand, is then likely experiencing great interference from the child's anxiety, unable to leave the child to go to the grocery store, spend time with friends, have individual time with another child, etc. These adjustments, made by the parent, are accommodations to the child's anxiety. Higher levels of accommodation are associated with worse treatment outcomes [88], so it is important for therapist working with anxious youth to address and help families reduce these behaviors.

Working with youth typically includes working with the parents [15]. Even when parents are not overly accommodating the youth's anxiety, they can be helpful in the therapeutic process. Therapists can coach parents on how to help their child use the skills learned in therapy when out of sessions. Therapists can also work with parents on how they can best support their child as they face anxiety-provoking situations. Parents may also be of help to the process by rewarding youth for approaching, rather than avoiding, things that make them anxious. As therapy progresses, parents may play an important role in facilitating exposure tasks at home. In this context, therapists may need to work with parents on how to address bad behaviors such as behavioral outbursts and may need to teach behavior management strategies (e.g., planned ignoring).

Conclusions and Future Directions

Anxiety disorders remain prevalent among children and adolescents and have been reported to be on the rise [89]. Some of these disorders present in similar ways as in adults, while others may present differently [90] or have slightly different diagnos-

tic criteria [11]. When working with youth, it is very important to take developmental considerations into account. This is true in assessment and diagnosis, as well as in treatment. Without proper consideration of these factors, clinicians are likely to miss important nuances of diagnosis and be less effective in treating these individuals. Although anxiety disorders may be less likely to be noticed by others compared to disorders that frequently present as behavioral problems (e.g., attention-deficit/hyperactivity disorder or oppositional defiant disorder), they remain a serious problem worthy of intervention.

Research supports the efficacy of CBT and SSRIs to treat children and adolescents with anxiety [17], and the treatment gains have been shown to be maintained years later [26, 90–92]. Nevertheless, some youth do not benefit fully from these treatments and remain symptomatic, and pediatric anxiety disorders may persist and be chronic [90]. This points to the need for further research to identify why these treatments do not benefit some youth, what treatment might be effective for those individuals, and what treatment would work best for different youth. In this vein, future research is needed to explore both the mechanisms of change within these interventions and the significant predictors of treatment outcome. With a better understanding, new treatments, based on theory and prior research, can be developed to help children and adolescents who do not currently benefit from CBT or SSRIs. Additionally, as noted earlier, further research is needed on alternate interventions, particularly parent therapies and acceptance-, mindfulness-, and meditation-based interventions, which have shown promise in previous research with adults.

As research in the field progresses, it is important that studies look at anxiety disorders and their treatment in youth, specifically. Although many features of the disorders and their treatments may span from childhood to adulthood, youth are not simply "little adults," and thus we cannot rely on the literature in adults or assume the features of the disorders and successful components of treatment remain stable over development [93, 94]. Future research should explore the pathways anxiety disorders may take, both in their presentation in childhood and adolescence, as well as how they may develop, progress, or change over the course of development.

References

1. Rosen JB, Schulkin J. From normal fear to pathological anxiety. Psychol Rev. 1998;105(2):325–50.
2. Copeland WE, Angold A, Shanahan L, Costello EJ. Longitudinal patterns of anxiety from childhood to adulthood: the Great Smoky Mountains study. J Am Acad Child Adolesc Psychiatry. 2014;53(1):21–33.
3. Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication – Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010;49(10):980–9.
4. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry. 2003;60(8):837–44.

5. Woodward LJ, Fergusson DM. Life course outcomes of young people with anxiety disorders in adolescence. J Am Acad Child Adolesc Psychiatry. 2001;40(9):1086–93.
6. Langley AK, Bergman RL, McCracken J, Piacentini JC. Impairment in childhood anxiety disorders: preliminary examination of the child anxiety impact scale–parent version. J Child Adolesc Psychopharmacol. 2004;14(1):105–14.
7. O'Neil KA, Puleo CM, Benjamin CL, Podell JL, Kendall PC. Suicidal ideation in anxiety-disordered youth. Suicide Life Threat Behav. 2012;42(3):305–17.
8. Swan AJ, Kendall PC. Fear and missing out: youth anxiety and functional outcomes. Clin Psychol. 2016;23(4):417–35.
9. Swan AJ, Kendall PC, Olino T, Ginsburg G, Keeton C, Compton S, et al. Results from the child/adolescent anxiety multimodal longitudinal study (CAMELS): functional outcomes. J Consult Clin Psychol. 2018;86(9):738–50.
10. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry. 1998;55(1):56–64.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Arlington: American Psychiatric Publishing; 2013.
12. Verduin TL, Kendall PC. Differential occurrence of comorbidity within childhood anxiety disorders. J Clin Child Adolesc Psychol. 2003;32(2):290–5.
13. Kendall PC, Compton SN, Walkup JT, Birmaher B, Albano AM, Sherrill J, et al. Clinical characteristics of anxiety disordered youth. J Anxiety Disord. 2010;24(3):360–5.
14. Palitz SA, Davis JP, Kendall PC. Treatment of anxiety in children and adolescents. In: Prinstein MJ, Youngstrom EA, Mash EJ, Barkley RA, editors. Treatment of childhood disorders, 4th edition. New York: Guilford Publications, Inc; in press. 2019;281–310.
15. Kendall PC, Hudson JL, Gosch E, Flannery-Schroeder E, Suveg C. Cognitive-behavioral therapy for anxiety disordered youth: a randomized clinical trial evaluating child and family modalities. J Consult Clin Psychol. 2008;76(2):282–97.
16. Silverman WK, Pina AA, Viswesvaran C. Evidence-based psychosocial treatments for phobic and anxiety disorders in children and adolescents. J Clin Child Adolesc Psychol. 2008;37(1):105–30.
17. Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med. 2008;359(26):2753–66.
18. Hollon SD, Beck AT. Cognitive and cognitive-behavioral therapies. In: Lambert MJ, editor. Bergin and Garfield's handbook of psychotherapy and behavior change. 6th ed. New York: Wiley; 2013. p. 393–442.
19. Kendall PC, Hedtke KA. Cognitive-behavioral therapy for anxious children: therapist manual. 3rd ed. Ardmore: Workbook Publishing; 2006.
20. Kendall PC, Hedtke KA. Coping cat workbook. 2nd ed. Ardmore: Workbook Publishing; 2006.
21. Kendall PC. Treating anxiety disorders in children: results of a randomized clinical trial. J Consult Clin Psychol. 1994;62(1):100–10.
22. Kendall PC, Choudhury M, Hudson J, Webb A. The C.A.T. Project manual for the cognitive-behavioral treatment of anxious adolescents. Ardmore: Workbook Publishing; 2002.
23. Kendall PC, Bjork R, Arnberg K, Neumer SP, Khanna M, Hudson J, et al. Mestringskatten for ungdom: Kognitiv atferdsterapi for ungdom med angst. Terapeutmanual. Oslo: Universitetsflorlaget; 2011.
24. Rapee RM, Lyneham HJ, Schniering CA, Wuthrich V, Abbott MA, Hudson JL, et al. Cool kids: child & adolescent anxiety program. Sydney: Centre for Emotional Health; 2006.
25. Gosch EA, Flannery-Schroeder E, Mauro CF, Compton SN. Principles of cognitive-behavioral therapy for anxiety disorders in children. J Cogn Psychother. 2006;20(3):247–62.
26. Kendall PC. Anxiety disorders in youth. In: Kendall PC, editor. Child and adolescent therapy: cognitive-behavioral procedures. 4th ed. New York: Guilford Press; 2012. p. 143–89.

27. Compton SN, March JS, Brent D, Albano AM, Weersing VR, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Adolesc Psychiatry. 2004;43(8):930–59.

28. Silk JS, Tan PZ, Ladouceur CD, Meller S, Siegle GJ, McMakin DL, et al. A randomized clinical trial comparing individual cognitive behavioral therapy and child-centered therapy for child anxiety disorders. J Clin Child Adolesc Psychol. 2018;47(4):542–54.

29. Kendall PC, Robin JA, Hedtke KA, Suveg C, Flannery-Schroeder E, Gosch E. Considering CBT with anxious youth? Think exposures. Cogn Behav Pract. 2005;12(1):136–48.

30. Peris TS, Compton SN, Kendall PC, Birmaher B, Sherrill J, March J, et al. Trajectories of change in youth anxiety during cognitive-behavior therapy. J Consult Clin Psychol. 2015;83(2):239–52.

31. Crawford EA, Frank HE, Palitz SA, Davis JP, Kendall PC. Process factors associated with improved outcomes in CBT for anxious youth: therapeutic content, alliance, and therapist actions. Cogn Ther Res. 2018;42(2):172–83.

32. Kendall PC, Beidas RS. Smoothing the trail for dissemination of evidence-based practices for youth: flexibility within fidelity. Prof Psychol Res Pract. 2007;38(1):13–20.

33. Kendall PC, Gosch E, Furr JM, Sood E. Flexibility within fidelity. J Am Acad Child Adolesc Psychiatry. 2008;47(9):987–93.

34. Villabø MA, Narayanan M, Compton SN, Kendall PC, Neumer S-P. Cognitive–behavioral therapy for youth anxiety: an effectiveness evaluation in community practice. J Consult Clin Psychol. 2018;86(9):751–64.

35. Comer JS, Puliafico AC, Aschenbrand SG, McKnight K, Robin JA, Goldfine ME, et al. A pilot feasibility evaluation of the CALM program for anxiety disorders in early childhood. J Anxiety Disord. 2012;26(1):40–9.

36. Hirshfeld-Becker DR, Masek B, Henin A, Blakely LR, Pollock-Wurman RA, McQuade J, et al. Cognitive behavioral therapy for 4-to 7-year-old children with anxiety disorders: a randomized clinical trial. J Consult Clin Psychol. 2010;78(4):498–510.

37. Barrett PM. Evaluation of cognitive-behavioral group treatments for childhood anxiety disorders. J Clin Child Psychol. 1998;27(4):459–68.

38. Hudson JL, Rapee RM, Deveney C, Schniering CA, Lyneham HJ, Bovopoulos N. Cognitive-behavioral treatment versus an active control for children and adolescents with anxiety disorders: a randomized trial. J Am Acad Child Adolesc Psychiatry. 2009;48(5):533–44.

39. Muris P, Meesters C, van Melick M. Treatment of childhood anxiety disorders: a preliminary comparison between cognitive-behavioral group therapy and a psychological placebo intervention. J Behav Ther Exp Psychiatry. 2002;33(3–4):143–58.

40. Shortt AL, Barrett PM, Fox TL. Evaluating the FRIENDS program: a cognitive-behavioral group treatment for anxious children and their parents. J Clin Child Psychol. 2001;30(4):525–35.

41. Silverman WK, Kurtines WM, Ginsburg GS, Weems CF, Lumpkin PW, Carmichael DH. Treating anxiety disorders in children with group cognitive-behavioral therapy: a randomized clinical trial. J Consult Clin Psychol. 1999;67(6):995–1003.

42. Bögels SM, Siqueland L. Family cognitive behavioral therapy for children and adolescents with clinical anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2006;45(2):134–41.

43. Ginsburg GS, Silverman WK, Kurtines WK. Family involvement in treating children with phobic and anxiety disorders: a look ahead. Clin Psychol Rev. 1995;15(5):457–73.

44. Crawley SA, Kendall PC, Benjamin CL, Brodman DM, Wei C, Beidas RS, et al. Brief cognitive-behavioral therapy for anxious youth: feasibility and initial outcomes. Cogn Behav Pract. 2013;20(2):123–33.

45. Öst L-G. One-session treatment for specific phobias. Behav Res Ther. 1989;27(1):1–7.

46. Chorpita BF, Weisz JR, Daleiden EL, Schoenwald SK, Palinkas LA, Miranda J, et al. Long-term outcomes for the child STEPs randomized effectiveness trial: a comparison of modular and standard treatment designs with usual care. J Consult Clin Psychol. 2013;81(6):999–1009.

47. Weisz JR, Chorpita BF, Palinkas LA, Schoenwald SK, Miranda J, Bearman SK, et al. Testing standard and modular designs for psychotherapy treating depression, anxiety, and conduct problems in youth: a randomized effectiveness trial. Arch Gen Psychiatry. 2012;69(3):274–82.

48. Crawford EA, Salloum A, Lewin AB, Andel R, Murphy TK, Storch EA. A pilot study of computer-assisted cognitive behavioral therapy for childhood anxiety in community mental health centers. J Cogn Psychother. 2013;27(3):221–34.

49. Khanna MS, Kendall PC. Computer-assisted cognitive behavioral therapy for child anxiety: results of a randomized clinical trial. J Consult Clin Psychol. 2010;78(5):737–45.

50. Spence SH, Holmes JM, March S, Lipp OV. The feasibility and outcome of clinic plus inter-net delivery of cognitive-behavior therapy for childhood anxiety. J Consult Clin Psychol. 2006;74(3):614–21.

51. March S, Spence SH, Donovan CL. The efficacy of an internet-based cognitive-behavioral therapy intervention for child anxiety disorders. J Pediatr Psychol. 2009;34(5):474–87.

52. Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JR, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2005;19(6):567–96.

53. Settipani CA, Brodman DM, Peterman J, Read KL, Hoff AL, Swan AJ, et al. Anxiety disor-ders in children and adolescents: assessment and treatment. In: Emmelkamp P, Ehring T, edi-tors. The Wiley handbook of anxiety disorders, volume II: clinical assessment and treatment. Chichester: Wiley-Blackwell; 2014. p. 1038–77.

54. Beidel DC, Turner SM, Sallee FR, Ammerman RT, Crosby LA, Pathak S. SET-C versus fluoxetine in the treatment of childhood social phobia. J Am Acad Child Adolesc Psychiatry. 2007;46(12):1622–32.

55. Birmaher B, Axelson DA, Monk K, Kalas C, Clark DB, Ehmann M, et al. Fluoxetine for the treatment of childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2003;42(4):415–23.

56. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. J Am Med Assoc. 2007;297(15):1683–96.

57. Ipser JC, Stein DJ, Hawkridge S, Hoppe L. Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev. 2009;3. Article No. CD005170.

58. Rynn MA, Riddle MA, Yeung PP, Kunz NR. Efficacy and safety of extended-release venlafax-ine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. Am J Psychiatry. 2007;164(2):290–300.

59. Rynn MA, Siqueland L, Rickels K. Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. Am J Psychiatr. 2001;158(12):2008–14.

60. Wagner KD, Berard R, Stein MB, Wetherhold E, Carpenter DJ, Perera P, et al. A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. Arch Gen Psychiatry. 2004;61(11):1153–62.

61. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. N Engl J Med. 2001;344(17):1279–85.

62. American Academy of Child and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2007;46(2):267–83.

63. Khanna MS, Carper MM, Harris MS, Kendall PC. Web-based parent-training for par-ents of youth with impairment from anxiety. Evid Based Pract Child Adolesc Ment Health. 2017;2(1):43–53.

64. Brinkmeyer MY, Eyberg SM. Parent-child interaction therapy for oppositional children. In: Kazdin AE, editor. Evidence-based psychotherapies for children and adolescents. New York: Guilford Press; 2003. p. 204–23.

65. Puliafico AC, Comer JS, Pincus DB. Adapting parent-child interaction therapy to treat anxiety disorders in young children. Child Adolesc Psychiatr Clin. 2012;21(3):607–19.

66. Choate ML, Pincus DB, Eyberg SM, Barlow DH. Parent-child interaction therapy for treatment of separation anxiety disorder in young children: a pilot study. Cogn Behav Pract. 2005;12(1):126–35.
67. Pincus DB, Santucci LC, Ehrenreich JT, Eyberg SM. The implementation of modified parent-child interaction therapy for youth with separation anxiety disorder. Cogn Behav Pract. 2008;15(2):118–25.
68. Lebowitz ER, Omer H, Hermes H, Scahill L. Parent training for childhood anxiety disorders: the SPACE program. Cogn Behav Pract. 2014;21(4):456–69.
69. Burke CA. Mindfulness-based approaches with children and adolescents: a preliminary review of current research in an emergent field. J Child Fam Stud. 2010;19(2):133–44.
70. Brown FJ, Hooper S. Acceptance and commitment therapy (ACT) with a learning disabled young person experiencing anxious and obsessive thoughts. J Intellect Disabil. 2009;13(3):195–201.
71. Semple RJ, Reid EF, Miller L. Treating anxiety with mindfulness: an open trial of mindfulness training for anxious children. J Cogn Psychother. 2005;19(4):379–92.
72. Biegel GM, Brown KW, Shapiro SL, Schubert CM. Mindfulness-based stress reduction for the treatment of adolescent psychiatric outpatients: a randomized clinical trial. J Consult Clin Psychol. 2009;77(5):855–66.
73. Britton WB, Lepp NE, Niles HF, Rocha T, Fisher NE, Gold JS. A randomized controlled pilot trial of classroom-based mindfulness meditation compared to an active control condition in sixth-grade children. J Sch Psychol. 2014;52(3):263–78.
74. Greco LA, Blackledge JT, Coyne LW, Ehrenreich J. Integrating acceptance and mindfulness into treatments for child and adolescent anxiety disorders: acceptance and commitment therapy as an example. In: Orsillo SM, Roemer L, editors. Acceptance and mindfulness-based approaches to anxiety: conceptualization and treatment. New York: Springer; 2010. p. 301–24.
75. Simkin DR, Black NB. Meditation and mindfulness in clinical practice. Child Adolesc Psychiatr Clin. 2014;23(3):487–534.
76. Nguyen TN, Nilsson S, Hellström A-L, Bengtson A. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. J Pediatr Oncol Nurs. 2010;27(3):146–55.
77. Dionigi A, Gremigni P. A combined intervention of art therapy and clown visits to reduce preoperative anxiety in children. J Clin Nurs. 2017;26(5–6):632–40.
78. Pifalo T. Pulling out the thorns: art therapy with sexually abused children and adolescents. Art Ther. 2002;19(1):12–22.
79. Stulmaker HL, Ray DC. Child-centered play therapy with young children who are anxious: a controlled trial. Child Youth Serv Rev. 2015;57:127–33.
80. Kendall PC, Makover H, Swan A, Carper MM, Mercado R, Kagan E, et al. What steps to take? How to approach concerning anxiety in youth. Clin Psychol. 2016;23(3):211–29.
81. Simeon JG, Ferguson HB. Alprazolam effects in children with anxiety disorders. Can J Psychiatry. 1987;32(7):570–4.
82. Simeon JG, Ferguson HB, Knott V, Roberts N, Gauthier B, Dubois C, et al. Clinical, cognitive, and neurophysiological effects of alprazolam in children and adolescents with overanxious and avoidant disorders. J Am Acad Child Adolesc Psychiatry. 1992;31(1):29–33.
83. Graae F, Milner J, Rizzotto L, Klein RG. Clonazepam in childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry. 1994;33(3):372–6.
84. Spiegel DA, Bruce TJ. Benzodiazepines and exposure-based cognitive behavior therapies for panic disorder: conclusions from combined treatment trials. Am J Psychiatr. 1997;154(6):773–81.
85. Velosa JF, Riddle MA. Pharmacologic treatment of anxiety disorders in children and adolescents. Child Adolesc Psychiatr Clin. 2000;9(1):119–33.
86. Shirk S, Saiz C. The therapeutic alliance in child therapy: clinical, empirical, and developmental perspectives. Dev Psychopathol. 1992;4(4):713–28.

87. Kagan ER, Frank HE, Kendall PC. Accommodation in youth with OCD and anxiety. Clin Psychol. 2017;24(1):78–98.
88. Gomes JB, Van Noppen B, Pato M, Braga DT, Meyer E, Bortoncello CF, et al. Patient and family factors associated with family accommodation in obsessive-compulsive disorder. Psychiatry Clin Neurosci. 2014;68(8):621–30.
89. Bitsko RH, Holbrook JR, Ghandour RM, Blumberg SJ, Visser SN, Perou R, et al. Epidemiology and impact of health care provider–diagnosed anxiety and depression among US children. J Dev Behav Pediatr. 2018;39(5):395–403.
90. Ginsburg GS, Becker-Haimes EM, Keeton C, Kendall PC, Iyengar S, Sakolsky D, et al. Results from the child/adolescent anxiety extended long-term study (CAMELS): primary anxiety outcomes. J Am Acad Child Adolesc Psychiatry. 2018;57(7):471–80.
91. In-Albon T, Schneider S. Psychotherapy of childhood anxiety disorders: a meta-analysis. Psychother Psychosom. 2007;76(1):15–24.
92. Gibby BA, Casline EP, Ginsburg GS. Long-term outcomes of youth treated for an anxiety disorder: a critical review. Clin Child Fam Psychol Rev. 2017;20(2):201–25.
93. Hudson JL. Mechanisms of change in cognitive behavioral therapy for anxious youth. Clin Psychol. 2005;12(2):161–5.
94. Kingery JN, Roblek TL, Suveg C, Grover RL, Sherrill JT, Bergman RL. They're not just "little adults": developmental considerations for implementing cognitive-behavioral therapy with anxious youth. J Cogn Psychother. 2006;20(3):263–73.

Chapter 8
Anxiety Disorders in Emerging Adulthood

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Emerging Adulthood

Emerging adulthood (EA) describes the developmental stage that spans from the end of adolescence (age 18) to the beginning of adulthood (ages 25–30) in high-income countries [1, 2]. This life stage is not universal throughout history or across cultures. Rather, it is the result of shifting societal norms since the mid-twentieth century that have led many individuals to postpone marriage and parenthood in favor of pursuing higher education and career prospects [2]. These societal changes have allowed young people to experience a period of identity exploration in their 20s before adopting adult roles and responsibilities in their 30s [1, 2].

EA is characterized by both excitement and stress. Many EAs have yet to commit to a career or long-term romantic partner and are therefore afforded greater freedom to explore different identities in the domains of work, love, and worldview [2]. However, these changes and opportunities cause this life stage to be inherently unstable. Many EAs switch jobs numerous times, which results in a high degree of

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geographically mobility [1, 2]. EAs also typically begin and end several romantic relationships before choosing a long-term romantic partner [1, 2]. These changes can leave EAs feeling stressed and socially isolated. Thus, EA is a stage characterized by identity exploration, experimentation, instability, and a sense of being in between [3]. These feelings usually peak in the early 20s and decline by the age of 30 [3].

EA is also a critical period for the prevention, early detection, and treatment of mental illness. Epidemiological research shows that the majority of mental disorders have a median age of onset before or during EA [4]. Thus, many individuals will experience mental health problems for the first time during this stage. Furthermore, untreated mental illness during EA can have deleterious consequences for individuals' educational attainment, career, and interpersonal relationships, and these negative effects can persist across the lifespan [5]. The prevention and treatment of mental illness during EA is therefore paramount from a public health perspective.

In this chapter, we will discuss the phenomenology and treatment of anxiety disorders in EA, as anxiety disorders affect approximately 22.3% of individuals during this life stage [6]. We will first review biological, psychological, and social transitions that occur during EA and discuss ways that these transitions may contribute to the onset of anxiety disorders. We will then present data on the epidemiology of anxiety disorders during EA and discuss factors that are associated with increased risk for anxiety disorders during EA. Finally, we will review considerations for the treatment of anxiety disorders in EA.

Biopsychosocial Development in Emerging Adulthood

EA is a distinct period of human development that involves complex changes in neurobiological, psychological, and social systems. The instability provoked by these changes may trigger the onset or worsening of anxiety in vulnerable individuals. Conversely, individuals with preexisting anxiety may struggle to navigate important developmental transitions during this life stage, leading to increased symptoms and associated impairment.

Neurobiological Development Human neurodevelopment continues throughout adolescence and EA, particularly in brain regions that support higher-order cognitive processes such as reasoning, planning, emotion regulation, and social cognition [7]. For example, cross-sectional studies show evidence of decreasing gray matter and increasing white matter in the frontal cortex between adolescence and EA [8, 9]. These changes likely reflect synaptic pruning and the myelination of axons in the frontal cortex; both of which support more efficient processing in this region [7]. In addition, these changes enable enhanced top-down control of limbic regions, which contributes to improved decision-making and emotion regulation capabilities during EA [7]. Maturation in the medial prefrontal cortex (mPFC) and inferior parietal lobule also leads to enhanced social cognitive abilities, such as improved perspective taking [10]. Finally, adolescents and EAs show heightened mPFC activity in

response to social cues compared to children, which coincides with an increase in self-conscious emotions during this life stage [11]. These neurodevelopmental changes likely enable EAs to navigate complex adult contexts, including work environments and romantic relationships.

However, these neurodevelopmental changes may set the stage for the onset of mental disorders, including anxiety disorders, in adolescents and EAs [7]. For example, limbic regions (e.g., amygdala and accumbens) mature in adolescence before prefrontal control regions, thereby creating a temporary imbalance in emotion regulation circuits [12–14]. This imbalance may trigger the onset of mental disorder (especially substance use and affective disorders) in adolescents with preexisting risk [7, 12]. As the prefrontal cortex continues to develop in EA, top-down control of limbic regions increases and EAs become more adept at integrating information about future risks when making decisions [7]. Though typically adaptive, this increasing motivation to avoid situations with possible negative outcomes may also contribute to the onset of anxiety disorders [7]. Finally, enhanced perspective taking and self-conscious emotions in EA may precipitate or augment social anxiety symptoms, as social anxiety disorder (SAD) is associated with a heightened focus on the mental states of others [15].

Psychological Development

Emotion Regulation   Emotion regulation abilities also mature during EA, supported by the neurodevelopmental changes described above. For example, EAs demonstrate increasing capacity to plan for the future and to consider the consequences of their actions when making decisions [16]. These abilities are necessary for EAs to achieve developmental milestones such as educational attainment and financial independence. EAs also demonstrate increasing competence in the use of emotion regulation skills. For example, research indicates that EAs are more likely to use adaptive emotion regulation strategies (e.g., social support seeking) compared to adolescents [17], and the use of reappraisal (an adaptive emotion regulation skill) increases between EA and older adulthood [18]. However, EAs also use negative emotion regulation strategies such as passivity and avoidance at rates comparable to adolescents [17]. Taken together, these findings suggest that EA is characterized by improvements in emotion regulation abilities, but that these skills continue to develop into adulthood. EAs who struggle to hone these skills may be at risk for mental health problems. For example, researchers have observed that adaptive emotion regulation skill use prospectively predicts lower levels of anxiety and depression among EAs [19].

Identity   EA is also a critical period for identity exploration and commitment. This stage is often characterized by limited parental oversight and responsibility and is therefore an ideal time for individuals to explore different identities in work, love, and worldview [2]. In addition, EAs may explore same-sex and/or other-sex behav-

iors and adopt a sexual identity label during this life stage [20]. The process of identity exploration can be both exciting and stressful for EAs. For example, failure experiences in school, work, or romantic relationships may cause anxiety and worry in these domains [2], and sexual minority EAs may encounter discrimination and/or victimization that leads to distress [20]. Specific identity exploration processes, such as rumination about identity choices, have also been linked with psychopathology [21]. Finally, elevated levels of anxiety in EAs are associated with identity disturbance [22, 23] and difficulty in making identity commitments during this developmental stage. For example, in one study, EAs with high shyness and anxiety reported lower levels of identity commitment compared to their peers [24]. These studies suggest that anxiety may thwart identity development for EAs, particularly if avoidance limits their participation in specific life domains [24].

Social Development

Higher Education   The majority of EAs in the USA (approximately 70%) enter some form of tertiary education after high school [25]. Higher education provides EAs with an opportunity to explore different identities and to build friendships with peers [25]. However, EAs also experience high levels of stress in college settings, which can have a negative effect on their mental health. For example, anxiety and depression symptoms have been shown to increase throughout the first year of college [26]. Factors such as academic stress, disengagement from studies, and loneliness are all associated with psychological distress in college [27]. In addition, sleep disturbance and anxiety are reciprocally related in college students and can reinforce one another over time [28]. Thus, elements of the college environment (e.g., academic stress, social disconnection, sleep disruption) may lead to the onset or worsening of an anxiety disorder in vulnerable individuals.

Work and Unemployment   Many EAs explore different jobs during this life stage, with the ultimate goal of selecting a long-term occupation [2]. Research indicates that uncertainty about this process is associated with negative psychosocial outcomes. For example, uncertainty about the future and worry about money/unemployment are reciprocally related over time among EAs [29]. These findings suggest that EAs who have difficulty tolerating uncertainty about the future may engage in excessive worry as a coping response, which over time could develop into an anxiety disorder such as generalized anxiety disorder (GAD). Unemployment during EA is also a risk factor for mental health problems. Specifically, experiences of work disruption (i.e., being laid off, fired, or unemployed for an extended period) predict increasing depression symptoms among EAs [30]. Though the findings in this study were specific to depression and not anxiety, the stress associated with unemployment in EA could also precipitate the onset or worsening of an anxiety disorder.

Social Relationships   Finally, EAs must navigate significant change in their social relationships with family members and romantic partners. EAs typically engage in a

process of separation-individuation from their parents and, in so doing, develop a sense of self that is distinct from their family of origin [31]. Ideally, this process does not sever the bonds between EAs and their parents, but allows the relationship to evolve and become characterized by increasing mutuality over time [31, 32]. Parenting style and other family variables impact the success of this transition. For example, EAs' perceptions of parental support for their autonomy are associated with greater self-reported autonomy and social functioning during this life stage; and higher levels of autonomy and social functioning in EA are associated with lower anxiety and depression symptoms [33]. On the other hand, EAs who perceive their parents to be psychologically controlling report more problems with anxiety, depression, and vocational identity [33, 34]. Thus parental support of EAs' independence appears critical for fostering EAs' psychological adjustment and preventing anxiety.

EAs must also navigate profound change in the domain of romantic relationships. By late adolescence, many individuals are developmentally capable of having close, intimate bonds [35]. However, the median age of first marriage in most high-income countries is typically not until age 30 [1]. EA is therefore characterized by considerable fluidity in romantic relationships [35]. Cohabitation without long-term commitment, transient relationships (e.g., hookups), and periods of being unattached are all common during this life stage [35]. Researchers have proposed that EAs tend to prioritize their own economic and professional goals and only commit to a long-term relationship once they are able to balance their aspirations with the needs of a partner [35]. EAs' ability to navigate this transition appears predicated on strong interpersonal skills including insight, mutuality in relationships, and emotion regulation abilities [36]. EAs with weak skills in these areas report lower relationship satisfaction and higher levels of anxiety and depression [36].

In sum, EA is a life stage when individuals are separating from their families, but have yet to commit to a long-term romantic relationship. Many EAs therefore lack social support and are at risk for loneliness. Indeed, population prevalence data in Denmark [37], Australia [38], and the United Kingdom [39] indicate that EAs and the elderly are the age groups most affected by loneliness. Furthermore, a recent survey of 20,000 Americans demonstrated that the current cohort of EAs (i.e., Generation Z, those born from the mid-1990s to the mid-2000s) is the loneliest birth cohort in the USA [40]. The high prevalence of loneliness among EAs likely contributes to heightened vulnerability for mental health problems during this life stage (see [41, 42]). Furthermore, individuals with anxiety disorders in EA may struggle to establish and maintain high-quality relationships (see [43, 44]). In this way, loneliness and anxiety symptoms in EA may reinforce one another over time.

Epidemiology of Anxiety Disorders in Emerging Adulthood

Given the profound changes and challenges EAs face, it is no surprise that many experience mental illness. In the National Comorbidity Survey Replication (NCS-R), 43.8% of EAs in the USA met diagnostic criteria for a mental disorder in the

past year [6]. Furthermore, the anxiety disorders were the most commonly reported class of disorders (22.3%)[1] among EAs in the NCS-R [6]. Other epidemiological studies also indicate high rates of anxiety disorders among EAs. For example, in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), 11.9% of college students in the USA and 12.7% of their noncollege-attending peers met criteria for an anxiety disorder in the past year [45]. Finally, 21.5% of participants in the American College Health Association (ACHA) National College Health Assessment reported a past-year diagnosis of an anxiety disorder [46]. Taken together, these data indicate that anxiety disorders are highly prevalent among EAs in the USA, both in and out of the college environment.

Prevalence Rates of Specific Anxiety Disorders in EA Prevalence rates of anxiety disorders in EA vary by specific anxiety diagnosis. In the NCS-R, the most prevalent anxiety disorder among EAs was specific phobia (SP; 10.3%) followed by SAD (9.1%), adult separation anxiety disorder (ASAD; 4.0%), panic disorder (PD; 2.8%), GAD (2.0%), and agoraphobia (AG) without PD (1.0%; [6]). Prevalence rates were lower among college students assessed in the NESARC, but the most prevalent anxiety disorder was again SP (8.1%), followed by SAD (3.2%), PD (2.0%), and GAD (1.6%; [45]). Higher prevalence rates for PD and GAD were recently observed in an international sample of college students who were assessed as part of the World Mental Health International College Student Project (WMH-ICS; [47]). In this study, researchers used self-report screening scales to measure the prevalence of past-year mental disorders among first-year students at 19 colleges across eight countries [47]. Data from this study indicated a past-year prevalence of 16.7% for GAD and 4.5% for PD [47]. Thus SP, SAD, and ASAD appear especially prevalent among EAs, but PD, GAD, and AG are also observed at high rates during this life stage. The high prevalence rates of SP, SAD, and ASAD among EAs may be due to the fact that these disorders typically onset during childhood or adolescence [4]. In contrast, PD, GAD, and AG usually first appear during EA [4].

Outcomes Associated with Anxiety Disorders in EA Individuals who experience anxiety disorders before or during EA are at increased risk for negative outcomes. For example, data from the Great Smoky Mountains Study indicate the individuals with a childhood anxiety disorder diagnosis experience worse health and poorer financial and interpersonal functioning in EA [48]. In another study, researchers used data from the WMH-ICS to examine the relationship between mental health problems in college student and impairment in four domains: home management, college-related work, close relationships, and social life [49]. They found that the majority of participants with PD (60.6%) and GAD (53.1%) experience severe impairment in at least one domain [49]. Furthermore, when all mental disorders were considered in the same multivariate model, GAD and major depressive disorder (MDD) were the strongest predictors of impairment in college students [49].

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[1] This prevalence rate included obsessive-compulsive disorder and posttraumatic stress disorder, both of which were moved out of the anxiety disorder section in DSM-5.

Finally, the presence of an anxiety disorder in EA predicts heightened risk for anxiety and depression in later adulthood [50]. Thus prevention and early intervention programs for anxiety disorders in EA are needed.

Risk Factors for Anxiety Disorders in Emerging Adulthood

The development of prevention and early intervention programs for anxiety disorders in EA requires an understanding of the factors that increase vulnerability for these disorders. Much of the research on risk factors for anxiety disorders in EA has focused on childhood experiences, including childhood adversity, family relationships, and early symptoms. Less is known about the factors that precipitate the onset of anxiety disorders in EA. Each of these factors will be further discussed and examples provided.

Childhood Adversity Considerable research supports an association between childhood adversity and anxiety in adulthood. For example, data from the NCS-R indicate that a range of adverse experiences in childhood, including parental mental illness, parental substance abuse, parental criminality, family violence, physical abuse, sexual abuse, neglect, physical illness, and economic adversity, are all associated with greater odds of a lifetime anxiety disorder [51]. Furthermore, statistical models demonstrate that childhood adversities predict the onset of 28.7% of anxiety disorders in adolescence (ages 13–19), 31.3% of anxiety disorders in EA (ages 20–29), and 29.8% of anxiety disorder in later adulthood (age $\geq$ 30) [51]. These stable prediction rates suggest that the effect of childhood adversities on the development of anxiety disorder does not decline with age. In another study, researchers used latent profile analysis to examine risk profiles for mental health problems among college students [52]. They observed that participants with a financial risk profile (low childhood socioeconomic status and current financial strain) and a multiple risk profile (high childhood verbal abuse, recent negative life events, high neuroticism, and negative cognitive style) were at increased risk for anxiety symptoms in EA [52].

Insecure attachment may be one mechanism linking the experience of childhood adversities with anxiety in EA. In one study, researchers examined the relationship between childhood family experiences, attachment style, and past-year anxiety disorder diagnosis in a sample of EAs [53]. They found that parental neglect (i.e., parental disinterest in material and physical needs) and parental antipathy (i.e., parental hostility and rejection) predicted a diagnosis of an anxiety disorder in EA, but that parental antipathy emerged as the only significant predictor in a multivariate model [53]. Furthermore, an anxious attachment style (i.e., an attachment style characterized by a need for intimacy and a fear of rejection) mediated the association between parental antipathy and anxiety in EA [53]. An insecure attachment style could be problematic during EA if it interferes with the development of social bonds with peers and romantic partners, as these bonds support mental health dur-

ing this life stage [54, 55]. Indeed, insecure attachment is associated with heightened loneliness among college students [56], and loneliness in college students in turn predicts increased risk for anxiety [41].

Other Childhood Factors   In addition to childhood adversity and attachment style, other childhood factors such as childhood personality traits (i.e., habitual styles of behaving, thinking, and feeling) and childhood shyness (i.e., anxious preoccupation in social situations) predict risk for mental illness during EA. In one study, investigators examined the relationship between childhood personality traits and functioning during EA in the domains of academics, work, and social relationships [57]. The results of this study indicated that high conscientiousness, high agreeableness, high openness, and low neuroticism in childhood predicted better functioning in EA [57]. In another study, investigators examined changes in shyness from childhood (age 8) through adulthood (ages 30–35) and explored the relationship between shyness trajectories and mental health problems in adulthood [58]. They found that individuals whose shyness increased from childhood to adulthood were at heightened risk for SAD, MDD, alcohol use disorders, and substance use disorders in adulthood [58]. These data suggest that early symptoms of anxiety in childhood and adolescence predict risk for mental illness in adulthood.

Precipitants for Anxiety Disorders in EA   Much less is known about the factors that trigger the onset of anxiety disorders in EAs with underlying diatheses. However, EAs who struggle to navigate the developmental milestones discussed earlier (e.g., the transition to college or the work force) are probably at heightened risk for the onset of anxiety disorders. Our clinical experience also suggests that experimentation with drugs and alcohol can serve as a trigger for the onset of anxiety symptoms. Regular substance use is common during EA, with 59% of college students reporting alcohol use in the past month and 18% reporting cannabis use in the past month [46]. EAs who respond with fear to the physiological sensations triggered by substance use (e.g., cannabis use) may be at risk for developing anxiety disorders such as PD (see [59, 60]). Finally, social media use, particularly passive social media use, appears to be detrimental for mental health during this life stage and may be linked with the onset of anxiety. In one cross-sectional study of social media use in EAs, results showed that higher daily social media use was associated with a higher likelihood of having a probable anxiety disorder [61]. Furthermore, experimental research demonstrates that passive social media use (i.e., passively scrolling and browsing without posting) leads to declines in affective well-being on the same day [62]. Finally, researchers have demonstrated that psychological well-being declined among US adolescents between 2012 and 2016 and that these declines were preceded by an increase social media and internet use among adolescents [63]. Social media use may be beneficial for some EAs if it is used to facilitate in-person social interactions (see [64, 65]). However, researchers believe that social media use becomes detrimental if it replaces other activities (e.g., in-person social interactions, exercise, reading) that predict psychological well-being [63].

Treatment of Anxiety Disorders in Emerging Adulthood

Multiple empirically supported treatments (ESTs), including behavioral and pharmacological treatments, are available for adults with anxiety disorders, and these interventions are reviewed elsewhere in this volume (see Chaps. 12 and 13). EAs would have been included in the treatment trials that established the efficacy of these ESTs. However, we are aware of no systematic effort to explore EA as a predictor or moderator of treatment response in these trials. This omission is problematic, as EAs experience unique biological, psychological, and social changes that may impact their response to behavioral and pharmacological interventions. Below we discuss factors to consider when developing, testing, or delivering interventions to EAs with anxiety disorders.

Treatment Engagement and Retention EAs are notoriously challenging to engage and retain in mental health treatment, which appears to prevent many from receiving ESTs for anxiety disorders. Data from the NESARC indicate that only 16% of college students with a past-year anxiety disorder diagnosis received mental health treatment [45]. This treatment rate is much lower than the rate observed for college students with a past-year mood disorder diagnosis (34%; [45]), which suggests that EAs with anxiety disorders face unique barriers to accessing care. Commonly cited barriers to mental health treatment among college students include (1) the belief that stress is normal in college, (2) perceived lack of need for treatment, (3) the belief that the symptoms will improve naturally, and (4) perceived lack of time for treatment [66]. Thus EAs with persistent worry, social fears, or panic attacks may view these experiences as normative during an unstable life stage and be reticent to invest time and energy in mental health treatment. These barriers may also explain why EAs drop out of mental health treatment at rates higher than other age groups [67].

Targeted strategies are needed to reduce barriers to accessing and utilizing mental healthcare among EAs with anxiety disorders. For example, public education programs about anxiety disorders could reduce the perception among EAs that clinical anxiety is "normal stress." In addition, brief prevention and early intervention programs could be used to reach EAs during the initial stage of an anxiety disorder, before symptoms become entrenched. These brief programs might be more acceptable to EAs than the lengthy treatment regimens needed to address chronic disorders. Prevention programs for anxiety in childhood and adolescence have received preliminary empirical support [68] and should be studied in EAs. Programs that target specific risk factors for anxiety (i.e., selective prevention programs) or subclinical anxiety symptoms (i.e., indicated prevention programs) are likely to be most effective from a public health perspective. For example, cognitive behavioral and mindfulness-based interventions are both effective for reducing stress in university students [69] and could be studied as indicated prevention programs for anxiety among EAs. Internet- and mobile-based prevention and early

intervention programs could also be used to overcome time and logistic barriers to care, though more research on these programs is needed [70].

Clinicians treating EAs with anxiety disorders can also use evidence-based strategies to target patient engagement and treatment adherence. For example, researchers have developed a transdiagnostic intervention to increase EAs' motivation for treatment entitled Motivational Enhancement Therapy for Treatment Attrition (MET-TA; [71]). MET-TA was designed to address barriers to treatment retention among EAs, including poor working alliance and lack of knowledge about the structure and length of treatment [71]. To address these barriers, the MET-TA protocol prescribes the use of motivational interviewing techniques to explore the following themes during initial treatment sessions: (1) patient's reasons for seeking therapy, (2) patient's goals for therapy, (3) psychoeducation about the structure and length of therapy, (4) strategies to mitigate potential barriers to treatment engagement, and (5) a concrete plan to prevent early termination [71]. MET-TA was found to be feasible in an initial pilot trial; however, more research is needed to determine whether it is efficacious for reducing treatment attrition among EAs [71]. Nevertheless, the MET-TA protocol nicely illustrates the potential of motivational techniques to assess and mitigate EAs' barriers to treatment retention. The MET-TA protocol could also be beneficial for helping EAs explore motivation for pursuing age-appropriate goals that are challenging due to anxiety (e.g., interacting with professors, applying for jobs). Helping EAs approach these goals in treatment is important in order to reduce the likelihood that anxiety symptoms will thwart the achievement of developmental milestones.

Social Factors in Treatment Clinicians treating EAs with anxiety disorders should also consider the role of social factors in maintaining their patients' symptoms. If left unaddressed, these social factors can interfere with treatment response and lead to dropout. As noted, EA is a period of social transition, during which time individuals establish independence from the family of origin and move toward commitment in a long-term romantic relationship. EAs with anxiety disorders may present for treatment at different stages of this developmental process, with some still living with their parents and others struggling to navigate the nascent stages of marital relationships. Clinicians should therefore evaluate each patient's social context by asking questions about his or her living situation, frequency of contact with other individuals, and quality of relationships with family, friends, and romantic partners. Following this assessment, clinicians can reference the child anxiety literature as well as the adult anxiety literature to formulate whether and how social factors may be maintaining symptoms.

Specific relationship factors to address in treatment for EAs with anxiety disorders include overprotection, psychological control, criticism, and symptom accommodation. Parent overprotection has been studied in the child anxiety literature and appears to reinforce anxiety symptoms over time [72]. Though parent/partner overprotection has not been explicitly studied among EAs with anxiety disorders, it is probable that this behavior implicitly undermines EAs' self-efficacy and impedes recovery. Parent psychological control, which is defined as parental attempts to

influence children's behavior through manipulative tactics, has been studied in EAs and is associated with symptoms of both anxiety and depression [33, 73]. In addition, hostility and criticism from romantic partners have been linked with poorer psychotherapy response among adults with anxiety disorders [72, 74, 75]. Psychological control, criticism, and hostility from close others likely cause stress in patients with anxiety disorders, thereby exacerbating their symptoms and undermining their motivation for change [75]. These social factors are essential to address in treatment, either through a family session or referral for adjunctive family therapy, both of which are described below.

Clinicians should also assess and target symptom accommodation when treating EAs with anxiety disorders. Symptom accommodation occurs when close others (e.g., family, romantic partners) modify their behavior in order to prevent or reduce distress in a patient with a psychiatric disorder [76]. With regard to anxiety disorders, symptom accommodation often includes involvement in avoidance behaviors (e.g., grocery shopping for a patient with agoraphobia who fears the supermarket) or the provision of reassurance (e.g., assuring a patient with GAD that he will not be fired). If left unaddressed, symptom accommodation can undermine cognitive behavioral therapy for anxiety, as it prevent patients from approaching feared stimuli and learning they can tolerate the associated distress [72]. Indeed, symptom accommodation is associated with reluctance to seek treatment and treatment resistance among youth with obsessive-compulsive disorder [77]. Research on symptom accommodation in EAs is quite limited. However, researchers in one study observed an association between symptom accommodation by family and friends and social anxiety symptoms in college students [78]. More research is needed to explore symptom accommodation as a maintenance factor for anxiety among EAs, as well as strategies to reduce symptom accommodation in this population.

Clinicians who formulate that relationship factors may be maintaining a patient's symptoms may wish to incorporate the patient's family or partner into treatment. However, given that EA is a time when individuals value independence from both family and romantic partners (see [31, 35]), care should be taken to preserve the patient's autonomy when suggesting involving others in treatment. Clinicians can provide patients with psychoeducation about the interpersonal processes that reinforce anxiety and invite them to observe whether any of these patterns are present in their own relationships. If a patient observes a problematic interpersonal pattern, the clinician can invite relevant family members (with the patient's permission) for a psychoeducation session to address the unhelpful behavior. However, a single conjoint session may be insufficient to address entrenched interpersonal processes in some families. In these situations, clinicians may choose to refer the patient for adjunctive family therapy. For example, Family Focused Therapy for Anxiety Disorders (FFT-ADs) is a treatment that uses evidence-based assessment and intervention tools to reduce anxiety maintenance patterns within a family [75]. The treatment length can vary from 1 to 12 sessions and begins with an assessment of family hostility, criticism, and symptom accommodation [75]. The therapist then uses tools such as psychoeducation, communication enhancement training, problem-solving, and systematic reduction of symptom accommodation to help families reduce

anxiety-maintaining behaviors and enhance motivation for change [75]. FFT-AD has yet to be tested as an adjunct to empirically supported treatments for anxiety disorders [75]. However, the treatment is promising and the strategies that comprise the intervention may be helpful for clinicians working with EAs with anxiety disorders.

Assessment and Treatment of Co-occurring Substance Use Disorders Finally, clinical management of EAs with anxiety disorders should include a thorough psychiatric evaluation to assess for the presence of comorbid disorders, particularly substance use disorders (SUDs). In the NCS-R, SUDs were the second most prevalent class of disorders among EAs (after anxiety disorders), with 22.0% of EAs meeting criteria for a past-year SUD [6]. It is likely that the imbalance between developed limbic regions and immature prefrontal regions, discussed earlier, sets the stage for increased risk for SUDs during EA [79]. In addition, developmental stressors (e.g., college matriculation), reduced parental oversight, and increased environmental exposure to alcohol and drugs likely contribute to increased vulnerability for SUDs during this life stage [79]. Data from the NCS-R indicate that individuals with anxiety disorders have higher rates of SUDs [80], so EAs with anxiety disorders may be particularly at risk for problematic substance use. Little research exists to guide treatment recommendations for EAs with comorbid anxiety and SUDs. Integrated cognitive behavioral treatments that target anxiety and substance use symptoms simultaneously have been developed for adults, though evidence for these treatments is mixed [81, 82]. Instead, experts recommend referring EAs with comorbid anxiety and SUDs for evidence-based SUD treatment if they are willing [79]. On the other hand, if an EA expresses low readiness for SUD treatment, it may be useful to first engage the patient in evidence-based treatment for anxiety in order to foster awareness of the connection between emotions and substance use and to build motivation for change [79].

Future Research Directions

More research is needed to advance our understanding of the factors that lead to the onset and worsening of anxiety during EA. Given that EA was only recognized as a distinct developmental stage within the past 20 years, much work remains to be done to identify the myriad stressors associated with this stage and to determine which stressors are in fact causal risk factors for anxiety disorders. In addition, future studies should investigate the intraindividual processes that lead to the onset of anxiety disorders during EA. For example, it would be useful to examine the psychobiological processes that unfold within EAs in response to academic and social stress and lead to the development of anxiety symptoms and ultimately anxiety disorders. Researchers can explore this topic by using intensive time series data to examine the onset and maintenance of anxiety symptoms in vulnerable vs. resilient EAs. Finally, more research is needed to understand

whether extant findings derived from studies conducted with primarily white, college-attending EAs apply to other socioeconomic and cultural groups [83].

Even more pressing is the need for research to inform the clinical management of anxiety symptoms in EA. As noted, neurodevelopment continues throughout EA. Yet despite this fact, we are aware of no studies that have explored the interplay between pharmacological treatments for anxiety disorders and neurodevelopment during this life stage. For example, it is unclear whether unfolding brain changes impact the efficacy of established pharmacological treatments for anxiety in adults. Similarly, we are aware of no studies that have explored whether modifications are needed when delivering evidence-based interventions such as cognitive behavioral therapy to EAs with anxiety disorders. Finally, researchers should continue to develop and test prevention and early intervention programs for EAs who are at risk for anxiety disorders. Longitudinal studies with extended follow-ups are needed in order to examine whether treating subclinical anxiety symptoms during EA shifts the long-term course of anxiety disorders in adulthood.

Conclusion

EA describes the life stage that occurs from ages 18–30 in high-income countries and is a period of considerable neurobiological, psychological, and social development. These developmental changes are necessary in order to enable EAs to ultimately adopt adult roles and responsibilities. However, the myriad transitions during this life stage can be stressful and may precipitate the onset of mental health problems, including anxiety disorders, for some individuals. Indeed, approximately 22.3% of EAs meet criteria for an anxiety disorder in the past year [6], with those who experienced childhood adversity (e.g., abuse, neglect) being most at risk. Anxiety during EA can interfere with an individual's ability to attain developmental milestones, such as developing an independent identity and forming intimate social relationships. Adequate treatment of anxiety disorders in EA is therefore critical. Clinicians treating EAs with anxiety disorders should be attentive toward common issues that arise in treatment, including low treatment engagement, deleterious family factors (e.g., symptom accommodation), and comorbid substance use disorders. More research is needed to explore additional adaptations that could improve the efficacy of empirically supported treatments for anxiety disorders in EA.

References

1. Arnett JJ, Zukauskiene R, Sugimura K. The new life stage of emerging adulthood at ages 18–29 years: implications for mental health. Lancet Psychiatry. 2014;1:569–76.
2. Arnett JJ. Emerging adulthood: a theory of development from the late teens through the twenties. Am Psychol. 2000;55(5):469–80.

3. Skulborstad HM, Hermann AD. Individual difference predictors of the experience of emerging adulthood. Emerg Adulthood. 2016;4(3):168–75.
4. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602.
5. Henin A, Berman N. The promise and peril of emerging adulthood: introduction to the special issue. Cogn Behav Pract. 2016;23:263–9.
6. NCS. National Comorbidity Survey Replication (NCS-R) twelve-month prevalence estimates. 2007. http://www.hcp.med.harvard.edu/ncs/ftpdir/NCS-R_12-month_Prevalence_Estimates.pdf%5D
7. Taber-Thomas B, Perez-Edgar K. Emerging adulthood brain development. In: Arnett JJ, editor. The Oxford handbook of emerging adulthood. New York: Oxford University Press; 2016. p. 126–41.
8. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci. 2003;6(3):309–15.
9. Sowell ER, Thompson PM, Tessner KD, Toga AW. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. J Neurosci. 2001;21(22):8819–29.
10. Choudhury S, Blakemore S, Charman T. Social cognitive development during adolescence. Soc Cogn Affect Neurosci. 2006;1:165–74.
11. Somerville LH, Jones RM, Ruberry EJ, Dyke JP, Glover G, Casey BJ. The medial prefrontal cortex and the emergence of self-conscious emotion in adolescence. Psychol Sci. 2013;24(8):1554–62.
12. Casey BJ, Jones RM, Hare TA. The adolescent brain. Ann N Y Acad Sci. 2008;1124:111–26.
13. Eshel N, Nelson EE, Blair RJ, Pine DS, Ernst M. Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. Neuropsychologia. 2007;45:1270–9.
14. Mills KL, Godding A, Clasen LS, Giedd JN. The developmental mismatch in structural brain maturation during adolescence. Dev Neurosci. 2014;36:147–60.
15. Hezel DM, McNally RJ. Theory of mind impairments in social anxiety disorder. Behav Ther. 2014;45:530–40.
16. Steinberg L, Graham S, O'Brien L, Woolard J, Cauffman E, Banich M. Age differences in future orientation and delay discounting. Child Dev. 2009;80(1):28–44.
17. Zimmermann P, Iwanski A. Emotion regulation from early adolescence to emerging adulthood and middle adulthood: age differences, gender differences, and emotion-specific developmental variations. Int J Behav Dev. 2014;38(2):182–94.
18. John OP, Gross JJ. Health and unhealthy emotion regulation: personality processes, individual differences, and life span development. J Pers. 2004;72(6):1301–33.
19. Brewer SK, Zahniser E, Conley CS. Longitudinal impacts of emotion regulation on emerging adults: variable- and person-centered approaches. J Appl Dev Psychol. 2016;47:1–12.
20. Morgan EM. Contemporary issues in sexual orientation and identity development in emerging adulthood. Emerg Adulthood. 2012;1(1):52–66.
21. Beyers W, Luyckx K. Ruminative exploration and reconsideration of commitment as risk factors for suboptimal identity development in adolescence and emerging adulthood. J Adolesc. 2016;47:169–78.
22. Bogaerts A, Claes L, Vershueren M, Bastiaens T, Kaufman EA, Smits D, et al. The Dutch Self-Concept and Identity Measure (SCIM): factor structure and associations with identity dimensions and psychopathology. Personal Individ Differ. 2018;123:56–64.
23. Neacsiu AD, Herr NR, Fang CM, Rodriguez MA, Rosenthal MZ. Identity disturbance and problems with emotion regulation are related constructs across diagnoses. J Clin Psychol. 2015;71(4):346–61.
24. McNamara Barry C, Nelson LJ, Christofferson JL. Asocial and afraid: an examination of shyness and anxiety in emerging adulthood. J Fam Stud. 2013;19(1):2–18.

25. Arnett JJ. College students as emerging adults: the developmental implications of the college context. Emerg Adulthood. 2016;4(3):219–22.
26. Conley CS, Krisch AC, Dickson DA, Byrant FB. Negotiating the transition to college: developmental trajectories and gender differences in psychological functioning, cognitive-affective strategies, and social well-being. Emerg Adulthood. 2014;2(3):195–210.
27. Newcomb-Anjo SE, Villemaire-Krajden R, Takefman K, Barker ET. The unique associations of academic experiences with depressive symptoms in emerging adulthood. Emerg Adulthood. 2017;5(1):75–80.
28. Peltz JS, Rogge RD, Pugach CP, Strang K. Bidirectional associations between sleep and anxiety symptoms in emerging adults in a residential college setting. Emerg Adulthood. 2017;5(3):204–15.
29. Barlett ND, Barlett CP. Money and job worries as a function of emerging adulthood markers: an analysis of college-aged and adult populations using correlational and longitudinal designs. J Adult Dev. 2018;26:116–28.
30. Aseltine RH, Gore S. Psychosocial functioning following the transition from high school. J Adolesc Res. 2005;20(6):615–39.
31. Lapsley D, Woodbury RD. Social cognitive development in emerging adulthood. In: Arnett JJ, editor. The Oxford handbook of emerging adulthood. New York: Oxford University Press; 2016. p. 142–62.
32. Desjardins T, Leadbeater BJ. Changes in parental emotional support and psychological control in early adulthood: direct and indirect associations with educational and occupational adjustment. Emerg Adulthood. 2017;5(3):177–90.
33. Ingoglia S, Inguglia C, Liga F, Lo CA. Association between perceived parental psychological control and internalizing difficulties in emerging adulthood: the role of identity. J Soc Pers Relat. 2017;34(8):1227–40.
34. Lindell AK, Campione-Barr N, Killoren SE. Implications of parent-child relationships for emerging adults' subjective feelings about adulthood. J Fam Psychol. 2017;31(7):810–20.
35. Shulman S, Connolly J. The challenge of romantic relationships in emerging adulthood: reconceptualization of the field. Emerg Adulthood. 2013;1(1):27–39.
36. Davila J, Mattanah J, Bhatia V, Latack JA, Feinstein BA, Eaton NR, et al. Romantic competence, healthy relationship functioning, and well-being in emerging adults. Pers Relat. 2017;24:162–84.
37. Laasgard M, Friis K, Shevlin M. Where are all the lonely people? A population-based study of high-risk groups across the lifespan. Soc Psychiatry Psychiatr Epidemiol. 2016;51:1373–84.
38. Hawthorne G. Perceived social isolation in a community sample: its prevalence and correlates with aspects of peoples' lives. Soc Psychiatry Psychiatr Epidemiol. 2008;43:140–50.
39. Victor CR, Yang K. The prevalence of loneliness among adults: a case study of the United Kingdom. J Psychol. 2012;146(1–2):85–104.
40. Nemecek D, Cigna US. Loneliness index: Cigna; 2018.
41. Richardson T, Elliot P, Roberts R. Relationship between loneliness and mental health in students. J Public Ment Health. 2017;16(2):48–54.
42. Beutel MA, Klein EA, Brahler E, Reiner I, Junger C, Michal M, et al. Loneliness in the general population: prevalence, determinants, and relations to mental health. BMC Psychiatry. 2017;17:97.
43. Porter DL, Chambless DL. Social anxiety and social support in romantic relationships. Behav Ther. 2017;48:335–48.
44. Priest JB. Anxiety disorders and the quality of relationships with friends, relatives, and romantic partners. J Clin Psychol. 2013;69(1):78–88.
45. Blanco C, Okuda M, Wright C, Hasin DS, Grant BF, Liu S, et al. Mental health of college students and their non-college attending peers. Arch Gen Psychiatry. 2008;65(12):1429–37.
46. ACHA. American College Health Association – National College Health Assessment II: undergraduate student reference group data report Fall 2017. Hanover: American College Health Association; 2018.

47. Auerbach RP, Mortier P, Bruffaerts R, Alonso J, Benjet C, Cuijpers P, et al. The WHO world mental health surveys international college student project: prevalence and distribution of mental disorders. J Abnorm Psychol. 2018;127(7):623–38.
48. Copeland WE, Angold A, Shanahan L, Costello EJ. Longitudinal patterns of anxiety from childhood to adulthood: the great smoky mountain study. J Am Acad Child Adolesc Psychiatry. 2014;53(1):21–33.
49. Alonso J, Mortier O, Auerbach RP, Bruffaerts R, Vilagut G, Cuijpers P, et al. Severe role impairment associated with mental disorders: results of the WHO world mental health surveys international college student project. Depress Anxiety. 2018;35(9):802–14.
50. Gustavson K, Knudsen AK, Nesvag R, Kudsen GP, Vollset SE, Rechborn-Kjennerud T. Prevalence and stability of mental disorders among young adults: findings from a longitudinal study. BMC Psychiatry. 2018;18(65):1–15.
51. Greif Green J, McLaughlin KA, Berglund P, Gruber MJ, Sampson NA, Zaslavsky AM, et al. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2010;67(2):113–23.
52. Newcomb-Anjo SE, Barker ET, Howard AL. A person-centered analysis of risk factors that compromise wellbeing in emerging adulthood. J Youth Adolesc. 2017;46:867–83.
53. Schimmenti A, Bifulco A. Linking lack of care in childhood to anxiety disorders in emerging adulthood: the role of attachment styles. Child Adolesc Mental Health. 2015;20(1):41–8.
54. Moore LE, Shell MD. The effects of parental support and self-esteem on internalizing symptoms in emerging adulthood. Psi Chi J Psychol Res. 2017;22(2):131–40.
55. Heinze JE, Cook SH, Wood EP, Dumadag AC, Zimmerman MA. Friendship attachment style moderates the effect of adolescent exposure to violence on emerging adult depression and anxiety. J Youth Adolesc. 2018;47:177–93.
56. DiTommaso E, Brannen-McNulty C, Ross L, Burgess M. Attachment styles, social skills, and loneliness in young adults. Personal Individ Differ. 2003;35:303–12.
57. Shiner RL, Masten AS. Childhood personality as a harbinger of competence and resilience in adulthood. Dev Psychopathol. 2012;24:507–28.
58. Tang A, Van Lieshout RJ, Lahat A, Duku E, Boyle MH, Saigal S, et al. Shyness trajectories across the first four decades predict mental health outcomes. J Abnorm Child Psychol. 2017;45:1621–33.
59. Zvolensky MJ, Bernstein A, Sachs-Ericsson N, Schmidt NB, Buckner JD, Bonn-Miller MO. Lifetime associations between cannabis, use, abuse, and dependence and panic attacks in a representative sample. J Psychiatr Res. 2006;40:477–86.
60. Zvolensky MJ, Lewinsohn P, Bernstein A, Schmidt NB, Buckner JD, Seeley J, et al. Prospective associations between cannabis use, abuse, and dependence and panic attacks and disorder. J Psychiatr Res. 2008;42:1017–23.
61. Vannucci A, Flannery KM, Ohannessian CM. Social media use and anxiety in emerging adulthood. J Affect Disord. 2017;207:163–6.
62. Verduyn P, Lee DS, Park J, Shablack H, Orvell A, Bayer J, et al. Passive Facebook usage undermines affective well-being: experimental and longitudinal evidence. J Exp Psychol Gen. 2015;144(2):480–8.
63. Twenge JM, Martin GN, Campbell WK. Decreased in psychological well-being among American adolescents after 2012 and links to screens time during the rise of smartphone technology. Emotion. 2018;18(6):765–80; Advanced online publication.
64. Shensa A, Sidani JE, Escobar-Viera CG, Chu K, Bowman ND, Knight JM, et al. Real-life closeness of social media contacts and depressive symptoms among university students. J Am Coll Heal. 2018;66(8):747–53.
65. Coyne SM, Padilla-Walker LM, Howard E. Emerging in a digital world: a decade review of media use, effect, ad gratifications in emerging adulthood. Emerg Adulthood. 2013;1(2):125–37.
66. Eisenberg D, Golberstein E, Gollust SE. Help-seeking and access to mental health care in a university student population. Med Care. 2007;45(7):594–601.

67. Edlund MJ, Wang PS, Berglund P, Katz SJ, Lin E, Kessler RC. Dropping out of mental health treatment: patterns and predictors among epidemiological survey respondents in the United States and Canada. Am J Psychiatr. 2002;159:845–51.
68. Lawrence PJ, Rooke SM, Creswell C. Review: prevention of anxiety among at-risk children and adolescents – a systematic review and meta-analysis. Child Adolesc Mental Health. 2017;22(3):118–30.
69. Regehr C, Glancy D, Pitts A. Interventions to reduce stress in university students: a review and meta-analysis. J Affect Disord. 2013;148:1–11.
70. Ebert DD, Cuijpers P, Munoz RF, Baumeister H. Prevention of mental health disorders using internet- and mobile-based interventions: a narrative review and recommendations for future research. Front Psychol. 2017;8:116.
71. Mistler LA, Sheidow AJ, Davis M. Transdiagnostic motivational enhancement therapy to reduce treatment attrition: use in emerging adults. Cogn Behav Pract. 2016;23:368–84.
72. Rapee RM. Family factors in the development and management of anxiety disorders. Clin Child Fam Psychol Rev. 2012;15:69–80.
73. Inguglia C, Ingoglia S, Liga F, Lo Coco A, Lo Cricchio MG, Musso P, et al. Parenting dimensions and internalizing difficulties in Italian and US emerging adults: the intervening role of autonomy and relatedness. J Child Fam Stud. 2016;25(2):419–31.
74. Chambless DL, Allred KM, Chen FF, McCarthy KS, Milrod B, Barber JP. Perceived criticism predicts outcome of psychotherapy for panic disorder: replication and extension. J Consult Clin Psychol. 2017;85(1):37–44.
75. Chambless DL. Adjunctive couple and family intervention for patients with anxiety disorders. J Clin Psychol In Session. 2012;68(5):548–60.
76. Lebowitz ER, Panza KE, Bloch MH. Family accommodation in obsessive-compulsive and anxiety disorders: a five-year update. Expert Rev Neurother. 2016;16(1):45–53.
77. Kagan ER, Frank E, Kendall PC. Accomodation in youth with OCD and anxiety. Clin Psychol Sci Pract. 2017;24:78–98.
78. Joogoolsingh N, Wu MS, Lewin AB, Storch EA. Social anxiety symptom accommodation in adults: phenomenology, correlates, and impairment. J Cogn Ther. 2015;29(1):3–19.
79. Bergman BG, Kelly JF, Nargiso JE. The age of feeling in-between: addressing challenges in the treatment of emerging adults with substance use disorders. Cogn Behav Pract. 2016;23:270–88.
80. Marmorstein N. Anxiety disorders and substance use disorders: difference associations by anxiety disorder. J Anxiety Disord. 2012;26:88–94.
81. Milosevic I, Chudzik SM, Boyd S, McCabe RE. Evaluation of an integrated group cognitive-behavioral treatment for comorbid mood, anxiety, and substance use disorders: a pilot study. J Anxiety Disord. 2017;46:85–100.
82. Hesse M. Integrated psychological treatment for substance use and comorbid anxiety or depression vs. treatment for substance use alone. A systematic review of the published literature. BMC Psychiatry. 2009;9:6.
83. Swanson JA. Trends in literature about emerging adulthood: review of empirical studies. Emerg Adulthood. 2016;4(6):391–402.

Chapter 9
Anxiety Disorders Among Older Adults: Empirically Supported Treatments and Special Considerations

Rachel Zack Ishikawa, Chirag Vyas, and Olivia Okereke

Introduction

Anxiety disorders are among the most common mental health problems for adults over the age of 60, and they are highly disabling. Late-life anxiety disorders increase the likelihood of functional decline, cognitive impairment, frailty, and medical comorbidities [1, 2]. Unfortunately, older adults suffering from anxiety disorders often fail to receive appropriate or adequate treatment. More than two thirds of adults with late-life anxiety receive no treatment at all [3]. When empirically supported treatments for anxiety disorders in general clinical populations are provided, those treatments typically fail to address the specific needs of older adults. Furthermore, while many older adults respond to standard anxiety treatments, others require augmented or combined treatment to attain adequate responses.

In this chapter, we will first discuss the prevalence and treatment of anxiety disorders among older adults. Then, we will present four common targets for augmentation of standard treatments for late-life anxiety, as tailoring anxiety treatment is likely to improve treatment effectiveness among older adults. These key areas are cognitive impairment, age-related socioemotional changes, medical comorbidities, and treatment underutilization.

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Prevalence and Key Clinical Features of Anxiety Disorders Among Older Adults

According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [4], anxiety disorders affecting adults include generalized anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, and specific phobia. Estimates of the rates of anxiety disorders among older adults vary widely, from 1% to 17% for any anxiety disorder among community samples and 1–28% among clinical samples [5–7].

Previous research has suggested that the prevalence of anxiety disorders decreases with age, with lower rates among the oldest-old (ages 85+) compared to the younger-old (60 or 65–74) [5, 8]. However, recent research has challenged this finding and suggests that prior estimates may have reflected misclassification of anxiety in older adults due to various factors, including different definitions of anxiety across cohort groups, different age cutoffs used, and/or variation of illness presentation over time [9].

To illustrate the impact of the definition of anxiety on age-related rates, researchers from the Survey of Health, Ageing, and Retirement in Europe (SHARE) [2] examined anxiety as a dimensional rather than a categorical construct and found that rates increased, rather than decreased, after age 70. Furthermore, dimensional versus categorical analysis provides evidence of a changing symptom profile with age. When Meloyan and colleagues [10] examined anxiety components separately, some symptoms (autonomic arousal, muscle tension, irritability) decreased with age; others (worry, fatigue) increased with age; others (concentration and sleep difficulties) remained stable across age groups.

Regarding risk indicators and correlates of late-life anxiety, several factors appear to be stable across studies. Research shows that adults of any age who are of lower socioeconomic status, lower education, and female sex are more likely to be anxious [2, 10]. Among older adults, anxiety is more likely among those who report losses in physical, cognitive, and psychosocial functioning and increases in medical conditions, pain, and negative life events [2, 11]. While discussed here as a disorder of later-life, it is worth noting that – like most psychiatric disorders – anxiety generally tends to have onset earlier in the lifespan: 90% of older adults with a primary anxiety disorder developed that disorder before the age of 41 [12], and median first onset is typically in the second decade of life [13].

Anxiety Treatments Among Older Adults

Both psychotherapy and psychopharmacology have shown promise for the treatment of late-life anxiety disorders. Before reviewing the current findings regarding the efficacy of these treatments, it is important to note two considerations. First, the majority of intervention research of non-adapted treatments involves relatively

healthy, "young-old" (typically ages 65–74) participants without cognitive decline or other major medical comorbidities; thus, these treatments may not be generalizable to the "old" (74–85) and "oldest-old" (85+) who are more likely to be cognitively impaired and/or to have chronic medical conditions. Second, the extant studies have primarily addressed treatment for GAD. Thus, less is known about the efficacy of interventions for other anxiety disorders.

Empirically Supported Psychotherapy

Cognitive behavioral therapy (CBT) has been supported as the first-line treatment for late-life anxiety (see Chap. 12). It has demonstrated greater efficacy for reducing anxiety, worry, and depression, compared with both passive and active control conditions [14]. The standard components of CBT include psychoeducation, monitoring of thoughts and emotions, relaxation training, cognitive restructuring, and exposure to sources of anxiety. Telephone-delivered CBT has also shown promise for reducing worry and overall symptoms of GAD among older adults [15].

Components of CBT for anxiety – relaxation training and behavioral activation – may also be offered as stand-alone treatments. Relaxation strategies such as music intervention, yoga, and progressive muscle relaxation training were found to be most beneficial for reducing anxiety symptoms [16]. Behavioral activation, which involves engaging in previously avoided pleasurable or meaningful activities and monitoring adherence to healthy behaviors, has been shown to be effective for reducing loneliness and anxiety [17].

Psychopharmacologic Approaches

Over the last two decades, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have emerged as first-line treatments for anxiety disorders (see Chap. 13). Compared with some alternatives such as benzodiazepines (BZs), antidepressant medications are a safer alternative, with a lower risk profile, low risk of dependency or overdose, high tolerance, and efficacy in treating anxiety. A key clinical issue, however, is that the anxiolytic properties often take longer to achieve full effect in antidepressants; thus, many patients may require a brief overlap of their antidepressant treatment with anxiolytics. Evidence for classes of antidepressants used for management of late-life anxiety, as well as key clinical points, is summarized in Table 9.1. The referenced research focuses on adults ages 60 and older.

Briefly, SSRIs such as citalopram, escitalopram, and sertraline are among the most often studied for several anxiety disorders (GAD, social anxiety disorder, panic disorder), and they generally appear more favorable with regard to the balance of efficacy, safety, and tolerability when compared with tricyclic antidepressants (TCAs). SNRIs (serotonin and norepinephrine reuptake inhibitors) have also been

Table 9.1 Evidence for the use of antidepressant medications in the treatment of late-life anxiety disorders

Drug	Usual dose	Common known side effects	Known interaction	Comment	Clinical indication
SSRI [23–26]					
Escitalopram	5–20 mg/day	Hyponatremia (fatigue, delirium), GI effects (nausea, dry mouth, diarrhea), insomnia, agitation, headache, sexual dysfunction	SSRIs inhibit the hepatic cytochrome P-450 isoenzymes and should not be used in conjunction with medications that are metabolized by these isoenzymes (TCAs, steroids, benzodiazepines). Concurrent use with NSAIDs is associated with increased risk of upper GI bleeding	Citalopram, escitalopram, and sertraline are considered generally safe for older adults. Fluoxetine, paroxetine, and fluvoxamine may have higher risk of drug-drug interactions and therefore not recommended for elderly patients	Generalized anxiety disorder, post-traumatic stress disorder, panic disorder, social phobia
Citalopram	10–20 mg/day				
Sertraline	25–200 mg/day				
Paroxetine	10–40 mg/day				
Fluoxetine	10–60 mg/day				
SNRI [27–29]					
Duloxetine	10–60 mg/day	High blood pressure (venlafaxine), orthostatic hypotension (Duloxetine, Desvenlafaxine) nausea, dizziness, dry mouth	MAOIs, SSRIs, serotonergic drugs, NSAIDs	Less well tolerated than SSRIs. Duloxetine may worsen liver problems	Generalized anxiety disorder, post-traumatic stress disorder, panic disorder
Venlafaxine	37.5–225 mg/ day				
Desvenlafaxine	10–50 mg/day				
TCA [12, 30]					
Nortriptyline	10–150 mg/day	Postural hypotension, anticholinergic effects (dry mouth, urinary retention, confusion), cardiac abnormalities/ arrhythmias, sedation	MAOIs, SSRIs/medications that inhibit the hepatic cytochrome P-450 isoenzymes, anticholinergic agents	No specific studies of use of TCAs in older adults. Not recommended for elderly patients, especially amitriptyline, due to risk of cardiotoxicity and other side effects	Generalized anxiety disorder, panic disorder, social anxiety disorder
Amitriptyline	10–150 mg/day				
Imipramine	10–100 mg/day				
Desipramine	10–200 mg/day				

MAOI [31]					
Phenelzine	30–90 mg/day	Hypertensive crisis, drowsiness, dry mouth, headaches, weight gain (phenelzine), postural hypotension	Simultaneous use of MAOIs and SSRIs/TCAs can lead to serotonin syndrome. Hypertensive crisis can occur if ingestion of tyramine-rich foods takes place during MAOI treatment	In adult studies, found to be efficacious in panic and social anxiety disorder; studies did not separate findings by older vs. younger adults	Panic disorder, social anxiety disorder
Isocarboxazid	10–40 mg/day				
Selegiline	6–12 mg/day				
Tranylcypromine	10–30 mg/day				
Atypical [32]					
Bupropion	50–300 mg/day	Headache, dry mouth, nausea, insomnia, seizures	MAOIs, alcohol, medications that lower seizure threshold	Longer lag time to effectiveness. Several case reports – useful in agitation and anxiety in patients with dementia	Generalized anxiety disorder
Vortioxetine	5 mg/day	Nausea, constipation, dry mouth, somnolence	SNRIs, SSRIs, TCAs, MAOIs, NSAIDs	Limited evidence and mixed results. Enhance contextual and episodic memory and reverse memory deficits in the animal models	Generalized anxiety disorder
NaSSA [33]					
Mirtazapine	15–45 mg/day	Drowsiness, dry mouth, increased appetite, weight gain	MAOIs, SSRIs	Limited and inconsistent evidence in PTSD. Older patients may benefit from its effects on sleep and appetite	Post-traumatic stress disorder
BDs [34–36]					
Lorazepam	2–4 mg/day	Falls, hip fracture, cognitive impairment	SSRIs, CNS depressants, alcohol, medications that lower seizure threshold. Probenecid, antifungal medications such as itraconazole and ketoconazole, antiviral medications such as ritonavir, telaprevir, saquinavir	Usually prescribed for short periods of time. Quick acting and short-term benzodiazepines always preferred over long-term benzodiazepines	Panic disorder, generalized anxiety disorder, social anxiety disorder
Oxazepam	30–120 mg/day				
Alprazolam	0.75–4 mg/day				
Clonazepam	1–4 mg/day				
Diazepam	2 mg/day				

Abbreviations: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin and norepinephrine reuptake inhibitor, *TCA* tricyclic antidepressants, *MAOI* monoamine oxidase inhibitor, *NSAIDs* nonsteroidal anti-inflammatory drugs, *NaSSA* noradrenergic and specific serotonergic antidepressant, *BZ* benzodiazepine

studied for treatment of anxiety (GAD, panic disorder) but may be less well tolerated by some older adults. Buspirone is an atypical agent that has been in use for many years for anxiety treatment; its low side effect profile makes it an appealing choice for older adults. More limited data are available with respect to the use of other atypical agents (the antidepressants mirtazapine and bupropion) and MAOIs (monoamine oxidase inhibitors) specifically for late-life anxiety. See Table 9.1 for references. Finally, while not detailed in Table 9.1, other agent classes are sometimes used, typically by more experienced clinicians, separately from their FDA (Food and Drug Administration) indications [30]. For example, low doses of mood stabilizers/antiepileptic drugs, such as gabapentin, may be used in combination with other medications [18]; and beta-blockers, such as low-dose propranolol, in highly specific contexts such as situational specific or simple phobias [19] (e.g., performance anxiety or fear of flying). Table 9.1 is summarized based on evidence generally available among persons aged 60+ years.

Despite the ascendance of antidepressants as first-line therapy, for many decades prior to the advent of SSRIs and other antidepressants, clinicians relied on BZs for treatment of anxiety; this legacy continues to a large extent. BZs remain the most frequent class of medications prescribed to older adults and the most common treatment for late-life anxiety: 10–32% of all older adults are prescribed BZs, and prescription rates exceed 50% among adults with panic disorder [20]. Older adults are more likely than younger adults to use BZs and to use them long term [21]. This is a concern, given abundant evidence that BZ use increases risk among older adults for falls, hip fracture, impaired cognition, all-cause mortality, overdose, and misuse [20, 22–25]. Because of these risks, the American Geriatrics Society cautions against prescribing BZs to older adults [26].

Combined treatment of CBT and antidepressants appears to be an effective option. For example, CBT in combination with escitalopram has been shown to reduce elevated cortisol levels in older adults, which is postulated as a mechanism of anxiety that contributes to cognitive and physiological decline [27]. Similarly, CBT combined with paroxetine is a well-tolerated and effective treatment for panic disorder [28] and phobias [29].

Despite the effectiveness of the treatments described here, as few as 5% of adults with late-life anxiety disorders receive psychological treatment and 4% are prescribed an antidepressant [14]. This finding points to the need for health providers to be vigilant in recognizing anxiety disorders among their patients and to provide evidence-based treatment when treatment is warranted.

Age-Related Socioemotional Changes and Anxiety

Several key challenges common to older adults point to the need for augmentations to standard treatment for late-life anxiety. First, we address age-related socioemotional changes. These changes refer to the often unexpected emotional, physical, social, and lifestyle changes that frequently accompany aging. For many older

adults, these themes constitute the content of the worries that drive anxiety. Supporting older adults as they confront these changes – either within or in addition to standard anxiety treatments – and acknowledging their role in eliciting or exacerbating anxiety, may promote improvements in coping and acceptance. Schlossberg has proposed the term "mattering" as the need to feel important, needed, and depended on in older age [30]. We discuss that concept as well as socioemotional changes related to mortality and shifting relationships, each of which may elicit and maintain anxiety in older adults.

Aging often forces older adults to confront a changing sense of their own importance in the world or a decrease in one's sense of mattering. Shifts in the perception of mattering often occur around specific role transitions, such as retirement, navigating relationships with adult children, and reconciling one's spiritual or religious beliefs, especially as they relate to death and dying [12]. Without grounding in accustomed professional or family roles, older adults often describe feeling adrift regarding personal identity. Some adults find new meaning in rewarding post-retirement work, volunteering, or relationships, which may protect against anxiety [31]. Others struggle to replace what they have lost.

For many older adults, anxiety relating to mortality is central to aging itself. Adults in the final 10, 20, or 30 years of life are confronted – at times suddenly, as in the case of an acute illness, and at other times more gradually – with the realization that they have already lived the majority of their lives and that life will end for them. Some individuals may become overwhelmed with regret, panic, or the fear of the unknown. Worries may take the form of doubt regarding the quality of one's life or about accomplishments or lack thereof. Illness or injury that previously elicited only minor concern may now signify an emergency and lead to catastrophic thinking [32], thereby escalating anxiety.

The third concept refers to shifts and losses in relationships (see Chap. 10). With aging comes loss: loved ones die, children move away, and work relationships become harder to maintain. Some older adults respond to these changes by cultivating new relationships, dating or remarrying, or moving closer to children. Others struggle with the weight of loneliness, itself strongly predictive of anxiety [33]. As adults age, they may look to relationships to satisfy needs that were previously met through work, children, or physical activities. As they do this, older adults may be frustrated by the high expectations placed on them to fulfill such a wide range of needs. The case of Barbara illustrates this shift:

Barbara is a 71-year-old married woman who retired 2 years ago from a senior corporate job, and has been married for 30 years to Ron. Barbara looked forward to retirement and the opportunity it would give her to pursue cycling and photography. She had not considered the role that Ron, already retired and spending most of his days at home, would play in her day-to-day life. Without their high-pressured careers to occupy them, Barbara realized that she and Ron had less in common than she had thought. Worse, she realized that their expectations and values about retirement did not align. Whereas Ron wanted Barbara at home, helping him research new recipes and preparing elaborate meals, Barbara preferred to exercise, eat healthfully, and be outdoors, activities she had never been able to prioritize while working. This misalignment created anxiety in Barbara, and doubts about how she would manage to share the next 10–20 years with her husband.

These shifts in mattering, perceptions of mortality, and relating inform the content of anxiety that many older adults bring to treatment. An effective treatment stance recognizes these age-related changes and responds accordingly. For example, a CBT therapist might encourage a patient to use cognitive restructuring to challenge negative assumptions about retirement and allow for hope and flexibility as the patient navigates the transition away from work. Exposure therapy can help patients with age-related physical decline differentiate fear-based avoidance from true physical limitations. And strategies such as "wisdom enhancement" and "redemptive sequences" [34] may be incorporated into problem-solving therapy to help patients access accumulated years of wisdom and previous experiences in which they coped effectively with stress.

Anxiety and Treatment Among Older Adults with Neurocognitive Disorders

Most adults remain cognitively intact throughout their lives. Although cognitive functioning typically shows some decline with old age, in approximately two thirds of adults, this decline will not impair functioning or independence. One third of adults, however, will develop a neurocognitive disorder that will adversely impact their memory and/or other cognitive domains, as well as their level of independence and functioning. The neurocognitive disorders encompass mild neurocognitive disorder (also referred to as mild cognitive impairment, or MCI), major neurocognitive disorder, and the dementias [35]. Common dementias include neurodegenerative diseases such as Alzheimer's disease, the most common dementia, vascular dementia, Lewy body disease, and frontotemporal dementia. In some cases, pathology from different dementias may overlap in the same individual (e.g., Alzheimer with Lewy body or vascular dementia).

Anxiety and cognitive impairment frequently co-occur. The odds of having symptoms of anxiety are increased by 1.4–3.6 among adults with MCI, compared with those with normal cognitive function [36], and impaired cognitive functioning and short-term memory are more likely among older adults with anxiety [37]. Longitudinal research has begun to examine the role of anxiety in the progression from MCI to dementia. This research shows that anxiety may be an independent risk factor for dementia [38, 39] as evidenced by the finding that clinically significant anxiety in midlife was associated with an increased risk in dementia at least 10 years later [40]. Furthermore, anxiety may be associated with increased rates of conversion from MCI to dementia [41].

Unfortunately, there is a dearth of research regarding the efficacy of psychotherapeutic treatments for anxiety disorders among older adults with cognitive impairment. Research supports the use of problem-solving therapy (PST), supplemented with compensatory strategies such as session notes, audio recording, and caregiver participation [42], for reducing anxiety and depression among

older adults with dementia as well as their caregivers. PST shows comparable effect when delivered in person or via video technology.

Mohlmann and colleagues [43] and Laidlaw [34] suggest adaptations to therapy such as offering shorter or more frequent sessions, encouraging note-taking or audio recording of sessions, and offering frequent repetitions and summaries. If cognitive material is too challenging, patients may benefit more from behavioral strategies, such as behavioral experiments or activity scheduling, with an emphasis on maintaining daily structure, pleasant events, and caregiver problem-solving [44].

Therapists working with cognitively impaired adults may also consider further adaptations such as treating the patient and caregiver together and exploring memories relevant to the specific patient, as is done in reminiscence therapy, spiritual care interventions, or music therapy [45, 46]. Preliminary research into newer therapies such as compassion-focused therapy, which emphasizes self-compassion to overcome self-criticism and shame, also shows promise in reducing symptoms of anxiety among people with dementia [47].

Caregiver support is critical. When adults assume a caregiver role for a parent, they suffer multiple losses: the loss of the parent they knew and the loss of their own independence. For caregivers, support groups and therapy can offer practical advice and an opportunity for caregivers to discuss stressors, burdens, and their experience of anticipatory grief, regrets, and guilt [45]. Caregiver interventions may also benefit the individuals being cared for [48], by enhancing the caregiver's skills and self-care and in some cases enabling them to increase the time they are able to keep their loved one at home.

Anxiety and Medical Comorbidities

Among older adults, anxiety disorders frequently co-occur with a number of medical conditions [7]. As many as 86% of adults over the age of 65 have at least one chronic medical condition [49], which puts them at increased risk for having an anxiety disorder [1]; when these adults also suffer from anxiety, they face complexities regarding diagnosis and treatment of the anxiety disorder itself as well as the comorbidity. The attribution of symptoms such as muscle tension, breathing problems, or sleep difficulties may be difficult to determine, and the hypervigilance that is often a hallmark of anxiety may cause patients and their physicians to misattribute physical symptoms to either anxiety or medical problems.

A strong association is found between anxiety and respiratory diseases, with the prevalence of anxiety as high as 75% [12, 50] among patients with respiratory disease. For patients with chronic obstructive pulmonary disease (COPD), anxiety exacerbates physical impairment, beyond that which an individual's pulmonary function might indicate. Patients with COPD and anxiety had poorer health outcomes, greater self-reported limitations, and higher risk of COPD symptoms [51]. Anxiety is also common among patients with cardiovascular disease (CVD),

with approximately 45% of adults with CVD reporting lifetime anxiety [52]. In addition, adults with anxiety may be at increased risk for developing CVD in the future [12].

The association between anxiety and respiratory and cardiovascular illnesses appears to be bidirectional. For example, the symptoms of COPD, particularly dyspnea, can resemble panic symptoms and may trigger panic attacks [53]. COPD treatments, such as beta agonists and theophylline-containing medications, may themselves exacerbate the symptoms of anxiety and panic [51]. Similarly, perceived physical limitations among congestive heart failure patients may exaggerate the influence of *contributing* factors (e.g., obesity, low physical activity), which may in turn increase the chances of cardiac complications [54]. For example, fear of overexertion may lead to the perception of physical impairment, and ultimately to activity restriction, which then increases the likelihood of deconditioning and other consequences of a more sedentary lifestyle. Another concern is the potential for undertreating symptoms. Specifically, physicians treating adults known to have anxiety may attribute physical complaints to anxiety, rather than medical issues, thereby increasing the risk of missing treatable medical problems [55].

Medical illness may complicate the treatment of anxiety disorders. For example, prior experience with cardiac or respiratory distress may impede the ability of a patient with panic disorder to follow the protocol for CBT for panic disorder. The symptom response of "doing nothing" that is taught in exposure protocols for treating panic makes little sense to a patient who may have legitimate cause for calling an ambulance. In treatment, care must be taken to help the patient differentiate symptoms of the illness from symptoms of a panic attack, so that patients are better able to respond appropriately. An example is shown with the case of James:

> James is a 68-year-old former firefighter with a history of congestive heart failure and panic disorder with agoraphobia. James had severe atrial fibrillation that required cardiac ablation, a sympathectomy, and a pacemaker. As a first responder, he and his medical history were familiar to other first responders in his community, and he feared travelling far from home *and* being treated by responders who did not know him. When his panic attacks began, he called his cardiologist with each attack, fearing that the attacks indicated cardiac distress. James's treatment first involved carefully observing and logging the symptoms of atrial fibrillation and panic attacks. He and his psychologist then developed a "cheat sheet" that identified the different symptom profiles of each condition, and the appropriate steps to take in each case. James carried a copy of this sheet with him and taped another copy to his refrigerator. He reported that it gave him a sense of control over both his panic and cardiac symptoms, and helped to decrease the burden and frequency of panic attacks.

Given the frequency of medical morbidity among older adults, providers are encouraged to view anxiety not as an inevitable side effect of comorbid conditions, but as a condition which, if treated successfully, may improve the trajectory of comorbid illness. Treatment for anxiety in the context of chronic illness focuses on reducing anxiety, improving coping and illness management, reducing illness-related stress, increasing social support, strengthening relationships, and improving quality of life. Treatment may also focus on spiritual and personal growth and on addressing end-of-life decisions and planning [56].

Utilization of Anxiety Treatment Among Older Adults

Age-related socioemotional changes, cognitive impairment, and medical comorbidities are common among older adults, and it is our hope that an improved understanding of the intersection of these factors with anxiety disorders will help clinicians to improve the outcomes for their patients. However, this opportunity is limited to those patients who actually seek and receive treatment. As noted earlier, this applies to fewer than one third of those adults suffering from anxiety. We will now examine barriers to treatment utilization faced by older adults who do not receive treatment and recommend interventions that have shown promise in reducing some of these barriers.

Barriers to obtaining mental health treatment occur at the patient, clinician, and system levels [57]. At the patient level, Patients may have difficulty accepting anxiety as a legitimate health problem and therefore may not consider mental health treatment as a potential solution. For example, in research among rural older adults, Brenes and colleagues [58] found that nearly 80% of adults surveyed with anxiety or depression believed they should not need help and that approximately 40% doubted that treatment would help. Stigma about psychiatric care, which is particularly strong among older minority patients and those with limited financial resources [59], may be a factor in this perception. At the level of the clinician, clinicians may create barriers to treatment if they fail to accurately detect anxiety disorders [60] or believe that anxiety is "just a part of ageing" [3]. System-level barriers to care may include long wait times, difficulties reaching clinicians by phone, and transportation challenges [61]. Importantly, system-level factors also include the dearth of geriatric psychiatrists and psychologists, and low Medicaid and Medicare reimbursements for mental health treatment, which limits the number of providers who accept public insurance [62].

A number of promising innovations aim to address these barriers. Telehealth technology holds promise for addressing practical barriers to receiving treatment, such as transportation, cost, and clinician availability [15]. Evidence suggests that this technology may be effective for older adults [63]. Another innovation, stepped care, is a system of mental health care delivery in which interventions of gradually increasing intensity are offered, if warranted, thus ensuring early detection and prioritization of the most complicated cases. van't Veer-Tazelaar and colleagues [64] showed that stepped care, involving a progression from watchful waiting to CBT-based bibliotherapy, problem-solving treatment, and finally referral to the general practitioner for medication, halved the incidence of new cases of depression and anxiety from 24% in the usual care group to 12% in the stepped care group.

Conclusion

The population of older adults is expected to reach 78 million by 2035 [65], which translates to millions of older adults suffering from anxiety disorders. Mental health and medical providers are responsible for ensuring that older adults are accurately

screened, diagnosed, and referred to the appropriate care and for knowing how to best meet the needs of older patients. Late-life anxiety is a treatable condition, yet proper identification and treatment can be complicated by socioemotional context, medical comorbidity, cognitive impairment, and treatment underutilization. Recognizing and attending to these factors – and knowing how to address them in treatment – will provide clinicians with the best chance of achieving optimal clinical outcomes for older adults with anxiety.

References

1. Gould CE, O'Hara R, Goldstein MK, Beaudreau SA. Multimorbidity is associated with anxiety in older adults in the health and retirement study. Int J Geriatr Psychiatry. 2016;31(10):1105–15.
2. Tetzner J, Schuth M. Anxiety in late adulthood: associations with gender, education, and physical and cognitive functioning. Psychol Aging. 2016;31(5):532–44.
3. Garrido MM, Kane RL, Kaas M, Kane RA. Use of mental health care by community-dwelling older adults. J Am Geriatr Soc. 2011;59(1):50–6.
4. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). Arlington: American Psychiatric Pub; 2013. 1 p.
5. Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML. High occurrence of mood and anxiety disorders among older adults: the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2010;67(5):489–96.
6. Canuto A, Weber K, Baertschi M, Andreas S, Volkert J, Dehoust MC, et al. Anxiety disorders in old age: psychiatric comorbidities, quality of life, and prevalence according to age, gender, and country. Am J Geriatr Psychiatry. 2018;26(2):174–85.
7. Remes O, Brayne C, van der Linde R, Lafortune L. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. Brain Behav. 2016;6(7):e00497.
8. Henderson AS, Jorm AF, Korten AE, Jacomb P, Christensen H, Rodgers B. Symptoms of depression and anxiety during adult life: evidence for a decline in prevalence with age. Psychol Med. 1998;28(6):1321–8.
9. Jeste DV, Blazer DG, First M. Aging-related diagnostic variations: need for diagnostic criteria appropriate for elderly psychiatric patients. Biol Psychiatry. 2005;58(4):265–71.
10. Miloyan B, Byrne GJ, Pachana NA. Age-related changes in generalized anxiety disorder symptoms. Int Psychogeriatr. Cambridge University Press. 2014;26(4):565–72.
11. Richardson TM, Simning A, He H, Conwell Y. Anxiety and its correlates among older adults accessing aging services. Int J Geriatr Psychiatry. 2011;26(1):31–8.
12. Wolitzky-Taylor KB, Castriotta N, Lenze EJ, Stanley MA, Craske MG. Anxiety disorders in older adults: a comprehensive review. Depress Anxiety. 2010;27(2):190–211.
13. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. American Medical Association. 2005;62(6):593–602.
14. Hendriks GJ, Oude Voshaar RC, Keijsers GPJ, Hoogduin CAL, van Balkom AJLM. Cognitive-behavioural therapy for late-life anxiety disorders: a systematic review and meta-analysis. Acta Psychiatr Scand. 2008;117(6):403–11.
15. Brenes GA, Miller ME, Williamson JD, McCall WV, Knudson M, Stanley MA. A randomized controlled trial of telephone-delivered cognitive-behavioral therapy for late-life anxiety disorders. Am J Geriatr Psychiatry. 2012;20(8):707–16.
16. Klainin-Yobas P, Oo WN, Suzanne Yew PY, Lau Y. Effects of relaxation interventions on depression and anxiety among older adults: a systematic review. Aging Ment Health. 2015;19(12):1043–55.

17. Burroughs H, Bartlam B, Ray M, Kingstone T, Shepherd T, Ogollah R, et al. A feasibility study for non-traditional providers to support the management of elderly people with anxiety and depression: the NOTEPAD study protocol. Trials. 2018;19(1):172.
18. Berlin RK, Butler PM, Perloff MD. Gabapentin therapy in psychiatric disorders: a systematic review. Prim Care Companion CNS Disord. 2015;17:5.
19. Steenen SA, van Wijk AJ, van der Heijden GJMG, van Westrhenen R, de Lange J, de Jongh A. Propranolol for the treatment of anxiety disorders: systematic review and meta-analysis. J Psychopharmacol. (Oxford). 2016;30(2):128–39.
20. Benítez CIP, Smith K, Vasile RG, Rende R, Edelen MO, Keller MB. Use of benzodiazepines and selective serotonin reuptake inhibitors in middle-aged and older adults with anxiety disorders: a longitudinal and prospective study. Am J Geriatr Psychiatr. 2008;16(1):5–13.
21. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiat. 2015;72(2):136–42.
22. Palmaro A, Dupouy J, Lapeyre-Mestre M. Benzodiazepines and risk of death: results from two large cohort studies in France and UK. Eur Neuropsychopharmacol. 2015;25(10):1566–77.
23. Wagner AK, Zhang F, Soumerai SB, Walker AM, Gurwitz JH, Glynn RJ, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? Arch Intern Med. 2004;164(14):1567–72.
24. Lader M. Benzodiazepines revisited – will we ever learn? Addiction. 2011;106(12):2086–109.
25. Maree RD, Marcum ZA, Saghafi E, Weiner DK, Karp JF. A systematic review of opioid and benzodiazepine misuse in older adults. Am J Geriatr Psychiatry. 2016;24(11):949–63.
26. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227–46.
27. Rosnick CB, Wetherell JL, White KS, Andreescu C, Dixon D, Lenze EJ. Cognitive-behavioral therapy augmentation of SSRI reduces cortisol levels in older adults with generalized anxiety disorder: a randomized clinical trial. J Consult Clin Psychol. 2016;84(4):345–52.
28. Hendriks GJ, Keijsers GPJ, Kampman M, Oude Voshaar RC, Verbraak MJPM, Broekman TG, et al. A randomized controlled study of paroxetine and cognitive-behavioural therapy for late-life panic disorder. Acta Psychiatr Scand. 2010;122(1):11–9.
29. Pachana NA, Woodward RM, Byrne GJA. Treatment of specific phobia in older adults. Clin Interv Aging. 2007;2(3):469–76.
30. Schlossberg NK. Revitalizing retirement. American Psychological Association: Washington, DC: Lifetools; 2009. 1 p.
31. Kypraiou A, Sarafis P, Tsounis A, Bitsi G, Andreanides E, Constantinidis T, et al. Depression and anxiety in Greek male veterans after retirement. Mil Med. 2017;182(3):e1639–44.
32. Vehling S, Kissane DW. Existential distress in cancer: alleviating suffering from fundamental loss and change. Psychooncology. 2018;27(11):2525–30.
33. Hyland P, Shevlin M, Cloitre M, Karatzias T, Vallières F, McGinty G, et al. Quality not quantity: loneliness subtypes, psychological trauma, and mental health in the US adult population. Soc Psychiatr Epidemiol. 2019;54(9):1089–99.
34. Laidlaw K, Kishita N. Age-appropriate augmented cognitive behavior therapy to enhance treatment outcome for late-life depression and anxiety disorders. GeroPsych. 2015;28(2):57–66.
35. Yochim B. Neurocognitive disorders in late life. In: Yochim B, Woodhead E, editors. Psychology of aging. New York: Springer Publishing Comapany; 2018. p. 201–22.
36. Yates JA, Clare L, Woods RT. Mild cognitive impairment and mood: a systematic review. Rev Clin Gerontol. 2013;23(04):317–56.
37. Schultz SK, Moser DJ, Bishop JR, Ellingrod VL. Phobic anxiety in late-life in relationship to cognition and 5HTTLPR polymorphism. Psychiatr Genet. 2005;15(4):305–6.
38. Gulpers B, Ramakers I, Hamel R, Köhler S, Oude Voshaar R, Verhey F. Anxiety as a predictor for cognitive decline and dementia: a systematic review and meta-analysis. Am J Geriatr Psychiatry. 2016;24(10):823–42.

39. Becker E, Orellana Rios CL, Lahmann C, Rücker G, Bauer J, Boeker M. Anxiety as a risk factor of Alzheimer's disease and vascular dementia. Br J Psychiatry. 2018;213(5):654–60.

40. Gimson A, Schlosser M, Huntley JD, Marchant NL. Support for midlife anxiety diagnosis as an independent risk factor for dementia: a systematic review. BMJ Open. 2018;8(4):e019399.

41. Mah L, Binns MA, Steffens DC. Alzheimer's disease neuroimaging initiative. Anxiety symptoms in amnestic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer disease. Am J Geriatr Psychiatry. 2015;23(5):466–76.

42. Kiosses DN, Alexopoulos GS. Problem-solving therapy in the elderly. Curr Treat Options Psychiatry. 2014;1(1):15–26.

43. Mohlman J, Gorenstein EE, Kleber M, de Jesus M, Gorman JM, Papp LA. Standard and enhanced cognitive-behavior therapy for late-life generalized anxiety disorder: two pilot investigations. Am J Geriatr Psychiatr. 2003;11(1):24–32.

44. Teri L, Logsdon RG, Uomoto J, McCurry SM. Behavioral treatment of depression in dementia patients: a controlled clinical trial. J Gerontol B Psychol Sci Soc Sci. 1997;52(4):P159–66.

45. Mast B. Clinical and person-centered perspectives on dementia assessment and care. San Francisco; 2018. p. 1–246.

46. Cheston R, Ivanecka A. Individual and group psychotherapy with people diagnosed with dementia: a systematic review of the literature. Int J Geriatr Psychiatry. 2016;32(1):3–31.

47. Craig C, Hiskey S, Royan L, Poz R, Spector A. Compassion focused therapy for people with dementia: a feasibility study. Int J Geriatr Psychiatry. 2018;33(12):1727–35.

48. Mittelman MS, Haley WE, Clay OJ, Roth DL. Improving caregiver well-being delays nursing home placement of patients with Alzheimer disease. Neurology. 2006;67(9):1592–9.

49. Smoller JW, Pollack MH, Wassertheil-Smoller S, Jackson RD, Oberman A, Wong ND, et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women's Health Initiative observational study. Arch Gen Psychiatry. 2007;64(10):1153–60.

50. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manag. 2006;31(1):58–69.

51. Eisner MD, Blanc PD, Yelin EH, Katz PP, Sanchez G, Iribarren C, et al. Influence of anxiety on health outcomes in COPD. Thorax. 2010;65(3):229–34.

52. Todaro JF, Shen B-J, Raffa SD, Tilkemeier PL, Niaura R. Prevalence of anxiety disorders in men and women with established coronary heart disease. J Cardiopulm Rehabil Prev. 2007;27(2):86–91.

53. Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. Eur Respir J. 2008;31(3):667–77.

54. Benderly M, Kalter-Leibovici O, Weitzman D, Blieden L, Buber J, Dadashev A, et al. Depression and anxiety are associated with high health care utilization and mortality among adults with congenital heart disease. Int J Cardiol. 2018;276:81–6.

55. Kogan JN, Edelstein BA, McKee DR. Assessment of anxiety in older adults: current status. J Anxiety Disord. 2000;14(2):109–32.

56. Satterfield JM. Minding the body workbook. Oxford: Oxford University Press; 2008. 1 p.

57. Alegria M, Alvarez K, Ishikawa RZ, DiMarzio K, McPeck S. Removing obstacles to eliminating racial and ethnic disparities in behavioral health care. Health Aff (Millwood). 2016;35(6):991–9.

58. Brenes GA, Danhauer SC, Lyles MF, Hogan PE, Miller ME. Barriers to mental health treatment in rural older adults. Am J Geriatr Psychiatry. 2015;23(11):1172–8.

59. Jimenez DE, Cook B, Bartels SJ, Alegria M. Disparities in mental health service use of racial and ethnic minority elderly adults. J Am Geriatr Soc. 2013;61(1):18–25.

60. Janssen EHC, van de Ven PM, Terluin B, Verhaak PFM, van Marwijk HWJ, Smolders M, et al. Recognition of anxiety disorders by family physicians after rigorous medical record case extraction: results of the Netherlands study of depression and anxiety. Gen Hosp Psychiatry. 2012;34(5):460–7.

61. Perreault M, Lafortune D, Laverdure A, Chartier-Otis M, Bélanger C, Marchand A, et al. Barriers to treatment access reported by people with anxiety disorders. Can J Psychiatr. 2nd ed. 2013;58(5):300–5.
62. Bishop TF, Press MJ, Keyhani S, Pincus HA. Acceptance of insurance by psychiatrists and the implications for access to mental health care. JAMA Psychiat. 2014;71(2):176–81.
63. Berryhill MB, Halli-Tierney A, Culmer N, Williams N, Betancourt A, King M, et al. Videoconferencing psychological therapy and anxiety: a systematic review. Fam Pract. 2018;36:53–63.
64. van't Veer-Tazelaar PJ, van HWJ M, van Oppen P, van HPJ H, van der Horst HE, Cuijpers P, et al. Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. Arch Gen Psychiatry. 2009;66(3):297–304.
65. United States Census Bureau. Older people projected to outnumber children for first time in U.S. history. 2018.

Chapter 10
Anxiety and Bereavement

Arielle Horenstein and Meredith E. Charney

Introduction

Bereavement, defined by the state of having lost a significant other, is one of the most painful and disruptive experiences an individual may face in a lifetime, and anxiety symptoms are a typical and natural part of the emotional response it evokes [1]. Anxiety during bereavement can be related to the loss itself or factors associated with the loss, such as the absence of a primary support person or companion, role changes and new demands (i.e., shifting from a shared to independent household), loss of a sense of safety or control, and/or confrontation with mortality. In addition, individuals who experience a loss are at risk for the development or worsening of an anxiety disorder, which may be associated with independent distress and impairment for the individual and serve as a potential obstacle to the natural grieving and healing process [1].

Although the literature indicates that many individuals experience anxiety following loss [2], anxiety among bereaved individuals is a relatively understudied phenomenon. As Shear and Skritskaya [1] note in their review on anxiety and bereavement, clinicians and researchers alike are often weary of pathologizing grief (i.e., the psychophysiological reaction that typically follows bereavement) or its associated reactions (e.g., anxiety), as it is expected and normal for an individual to experience a strong and negative affective reaction to the loss of a loved one. However, as they also indicate, the onset or worsening of anxiety symptoms and

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disorders in bereavement may not only contribute to additional suffering for the bereaved but may also complicate the grieving process and impede natural healing. Therefore, it is important to understand the experience of anxiety in the bereaved, including risk factors, potential long-term negative consequences, as well as the best course and methods of intervention.

In the following chapter, we will review the literature on the relationship between anxiety and bereavement. We will also discuss the known prevalence rates of both anxiety symptoms and anxiety disorders among bereaved individuals, common anxiety reactions following a loss, as well as research on predictors of anxiety during the post-loss period. In addition, we will discuss the associations between anxiety symptoms or disorders and complicated grief reactions. Finally, we will discuss potential areas for future research.

Prevalence of Anxiety Symptoms and Anxiety Disorders Among Bereaved Individuals

Studies suggest that there are high rates of elevated anxiety among bereaved adults. In a study conducted in Sweden, bereaved parents who had lost a child to cancer demonstrated an increased risk of clinical anxiety symptoms 4–6 years after the loss compared to non-bereaved parents [3]. Zisook et al. [2] found that anxiety symptoms were prominent for approximately 20% of a spousally bereaved sample and were significantly elevated both 2 months and 7 months post loss. In a study among 284 elderly survivors of an earthquake in China, bereavement due to the earthquake was associated with increased likelihood of reported anxiety symptoms indicative of a probable anxiety disorder (operationalized as a mean cumulative score higher than 2 on the Hopkins Symptom Checklist-25 anxiety subscale); compared to 21.3% of the non-bereaved sample, 52.7% of the bereaved sample reported anxiety symptoms at this level [4]. These findings extend to adolescent and young adult populations as well. For instance, in a recent study of adolescent and young adult oncology patients, having lost a parent was associated with elevated anxiety symptoms [5], and, in another large study of adolescents in Ireland, bereavement was also found to be a major risk factor of elevated anxiety symptoms [6].

Bereavement is also associated with an increased risk of an anxiety disorder diagnosis [4, 7–10]. A systematic review [10] found that, across studies, widowed individuals were at higher risk for both mood and anxiety disorders compared to non-bereaved individuals, including panic disorder (PD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD). The exact prevalence rate of anxiety disorders among bereaved individuals varies across studies and ranges anywhere from 7% to as high as 44%. A broad range of studies have found anxiety disorders, including GAD, PD, agoraphobia, social anxiety disorder (SAD), specific phobia, and PTSD, present in populations such as spousally bereaved individuals [11, 12] and caregivers to individuals who died from cancer [7], as well as bereaved

adults in Brazil [8] and European adults who lost a loved one in the 2004 Southeast Asian Tsunami [13]. In many of these studies, anxiety and related disorders are present not only immediately following the loss but also up to 6 years [11–13] following the loss.

Common Anxiety Reactions Following Loss

Reactions to loss are complex and multidimensional and may involve a range of experiences including anxiety, grief, and depressive symptoms. Although these symptom categories are overlapping, research has shown that these experiences represent distinct forms of emotional distress [14–16]. For instance, Prigerson et al. [14] first examined whether anxiety, depression, and grief symptoms represented three distinct symptom profiles among recently bereaved spouses. They found that anxiety did indeed represent a distinct cluster of symptoms (e.g., nervousness, fearfulness, irritation, somatization), separate from both depression (e.g., guilt, low mood, insomnia, apathy) and grief (e.g., yearning, searching, disbelief, feeling stunned). It is likely that in this study many bereaved individuals experienced these symptom clusters simultaneously; nevertheless, it is important to recognize that these symptoms represent distinguishable forms of distress following a loss, as they may require different forms of clinical intervention if they reach clinical levels of severity and impairment. Of course, not all individuals will necessarily experience anxiety or other forms of distress at clinically severe or impairing levels following a loss; for many, anxiety symptoms may co-occur with the natural grief response and naturally subside over time. However, it should not be assumed that this progression will necessarily be the case for all bereaved individuals.

For bereaved individuals who do experience anxiety at clinical levels of severity and impairment, the type of anxiety experienced seems to vary considerably as multiple distinct anxiety disorders are associated with bereavement. For instance, GAD, a disorder characterized by persistent and excessive worry about a number of different domains, and PD, a disorder characterized by unexpected and recurrent surges of intense fear and physical discomfort, are two of the most frequent anxiety disorders among the bereaved [10]. Other anxiety disorders that have been observed as having higher rates among bereaved individuals include agoraphobia, characterized by marked and disproportionate fear when confronted by certain situations (e.g., open spaces, crowded areas), and SAD, characterized by a fear of negative evaluation in social or performance situations. It is not yet clear from the existing literature whether specific loss-related factors lead to the development of these distinct anxiety disorders among the bereaved, or whether loss is simply a stressor that triggers the development of any disorder for which an individual has a preexisting vulnerability.

PTSD, although no longer formally considered an anxiety disorder in the DSM-5 [17], is also a commonly reported anxiety-related disorder among bereaved individuals, characterized by intrusive thoughts, negative emotions, avoidance, and/or

physiological arousal following the experience of witnessing a traumatic event. Unlike other anxiety disorders—for which little is known about the loss-specific mechanisms underlying their development among the bereaved—PTSD has clear loss-related origins, given that the loss itself is the index event that triggers its development. In addition, research suggests that PTSD may be more likely to develop following a loss if it is due to a violent, unexpected, or otherwise particularly traumatic death [12, 18–20]. For instance, Zisook et al. [12] found that only 10% of 350 bereaved widow and widowers who lost their spouse to chronic illness met criteria for PTSD 2 months after the loss, compared to a much higher percentage (36%) among those who lost their spouses to unnatural causes, such as suicide or accidents, suggesting that the circumstances surrounding the death likely play an instrumental role in the development of PTSD.

Overall, it is important to understand the nature of anxiety reactions following loss, so this form of distress is not overlooked due to assumptions that it reflects a typical grief response and/or will necessarily naturally subside over time. In addition, recognizing anxiety as distinct from other psychological reactions following a loss (e.g., grief) can help guide treatment recommendations when attending to a patient's anxiety and grief simultaneously. Similarly, correctly identifying distinct anxiety disorders among bereaved individuals has important implications for guiding intervention. Evidence-based treatments for disorders such as GAD, PD, and SAD, as well as PTSD, vary from each other and from other grief interventions. Therefore, distress among bereaved individuals needs to be correctly recognized so that, when warranted, bereaved individuals can be directed to the appropriate care.

Predictors of Anxiety and Anxiety Disorders in Bereavement

Numerous studies suggest that person-specific factors, such as psychiatric history, female gender, and grief-related cognitions, may predict elevated anxiety symptomatology following loss. In addition, circumstantial factors, such as relationship to the deceased, length of forewarning prior to the death, and suicide loss, may also predict anxiety symptomatology following loss.

An individual's mental health prior to loss predicts the incidence of both anxiety symptoms and anxiety disorders during bereavement [7, 11, 21]. One study found that, among caregivers of patients with cancer, better caregiver mental health prior to a loss of the patient predicted a lower incidence of both depressive and anxiety disorder diagnoses among caregivers post-loss [7]. Similarly, a study conducted among bereaved spouses found that the presence of PD and GAD at 6 months post-bereavement was best predicted by a past history of those disorders [11]. A past history of dysphoria, defined in one study as having experienced at least 1 week of depressed mood or irritability prior to the illness and death of a spouse, was also shown to predict elevated depressive symptoms, general anxiety symptoms, and feelings of hopelessness and helplessness over a 2-year post-loss

period [21]. Gender is another predictor of post-loss anxiety symptomatology, with women exhibiting higher anxiety, depression, and PTSD symptom severity [22, 23] following loss.

A bereaved individual's thoughts related to the death and their own grief are also associated with elevated anxiety following a loss. Specifically, studies show that threatening interpretations of grief (e.g., the belief that expressing one's emotions while grieving will lead to a loss of control), negative beliefs about the self (e.g., feelings of worthlessness or self-blame regarding the loss), and negative beliefs about the future (e.g., that there is no future without the deceased) explain a large degree of variance in anxiety symptoms in samples of bereaved adults [24, 25]. This suggests that the way an individual interprets their grief and the circumstances surrounding the death may play an important role in the degree of anxiety experienced post-loss. In particular, an individual's beliefs about the self, the future, and/or the consequences of grief are important cognitive targets of intervention for anxiety symptoms among bereaved individuals. Other studies on risk factors of anxiety symptoms among bereaved individuals focus on factors related to the loss itself, rather than person-specific variables. For instance, a study found that closely related survivors (e.g., spouses, parents, children, siblings) reported higher levels of depression and anxiety post-loss compared to distantly related survivors (e.g., in-laws, aunts/uncles, and nieces/nephews) [26], suggesting that degree of closeness to the deceased is an important predictor of elevated psychological symptoms, including anxiety, following bereavement. Loss by suicide is also a risk factor for elevated psychological distress including anxiety. A population-based study found that individuals who had lost a spouse to suicide were at elevated risk for multiple psychological disorders, including anxiety disorders and PTSD, compared to both the general population and to bereaved individuals who had loss a spouse by other outcomes [27]. Children and adolescents who lost a parent to suicide are also more likely to experience elevated anxiety symptoms immediately following the loss compared to those who were not suicide survivors [28].

Another loss-related predictor of anxiety among bereaved individuals is the degree of forewarning prior to the death. Most studies suggest that less forewarning about the death leads to greater anxiety. For instance, in a study conducted by Valdismarsdóttir et al. [29] among a sample of widows, those who had an awareness time of 24 hours or less of their husband's impending death from prostate cancer were at a much higher risk of experiencing anxiety compared to those who had an awareness time of 3–6 months. Keyes and colleagues [9] conducted a study within a population-based sample and found that, across all age groups, there was a heightened incidence risk for both PTSD and panic disorder among individuals who had experienced an unexpected loss compared to those who had experienced an expected loss. Although these studies suggest that unexpected loss is associated with greater anxiety, one study found the opposite to be the case. In Carr et al.'s [30] study among a large sample of older adult widowed individuals, prolonged forewarning of the death of a spouse (i.e., 6 months or more) was associated with elevated anxiety at both 6 and 18 months following the death. However, although Carr and colleagues found prolonged forewarning to be associated with higher general anxiety symp-

toms, sudden deaths were associated with a higher number of intrusive thoughts; this suggests that differing lengths of awareness time contribute to distinct anxiety and related symptom profiles (e.g., general anxiety symptoms versus traumatic stress symptoms). Overall, further study is needed to understand how anticipation of a loss is associated with anxiety symptoms during bereavement, including whether different lengths of awareness time are associated with distinct forms of anxiety and related symptoms.

Anxiety and Complicated Grieving

Bereavement may be a trigger for the onset or worsening of anxiety symptoms or disorders which may, in turn, interfere with the natural grieving and healing process [1]. For most individuals, acute grief is a time-limited period—typically lasting a period of weeks or months—immediately following a loss, during which an individual may experience feelings of intense yearning for the deceased, intrusive and distressing thoughts related to the death, and/or frequent pangs of grief. Following the acute grief period, it is often the case that the loss is then integrated into a bereaved person's ongoing life and, as the intensity of the pain decreases and thoughts related to the deceased become less dominant and intrusive, the individual is able to resume engagement in normal activities. However, this next stage of grief, often termed "integrated grief," does not occur for about 7% of bereaved individuals [31] wherein the natural grieving process is complicated and the experience of acute grief persists. In these cases, individuals continue to experience frequent and intense yearning for the deceased, frequent pangs of painful emotion, disbelief about the loss, as well as intrusive and distressing thoughts related to the death for prolonged periods of time. Individuals may avoid situations and activities that serve as reminders of the loss, contributing to further impairment. This type of prolonged grief is an increasingly well-recognized and well-studied phenomenon, often referred to in the literature as complicated grief (CG), prolonged grief disorder, or persistent complex bereavement disorder in the DSM-5 [17]. For the purposes of this chapter, we will refer to this kind of prolonged grief as complicated grief as that is where much of the literature has focused.

   Multiple studies demonstrate an association between anxiety symptoms or disorders and a higher degree of emotional distress during bereavement. For example, anxiety symptoms and disorders have been found to be associated with more severe grief and depression [11] and greater use of services [32] among bereaved spouses. Several longitudinal studies have also demonstrated that higher pre-loss anxiety symptoms are associated with greater grief intensity after a loss [33], and that the presence of anxiety symptoms immediately following a loss, including worry, prospectively predicts higher levels of anxiety, prolonged grief [34], and depression symptom severity [34, 35]. These studies highlight the importance of recognizing anxiety symptoms and disorders among bereaved individuals early on, as they may be associated with greater grief intensity and distress for prolonged periods of time following the loss.

Further, studies that have specifically examined the association between anxiety disorders and CG also show higher rates of anxiety disorders among bereaved individuals with CG compared to bereaved adults without CG [36]. Additional studies found that individuals with CG experience more panic spectrum symptoms compared to bereaved adults without CG [37], and that grief-related panic attacks are common among individuals with CG and are associated with greater CG symptom severity and impairment [38]. Finally, Sung et al. [39] found that among bereaved women with depression, an additional diagnosis of CG was associated with higher rates of panic disorder, PTSD, and SAD. Overall, these studies suggest that anxiety disorders and CG commonly co-occur. However, the mechanism of action is not well understood; as such, it is unknown whether the presence of anxiety disorders serve as a risk factor for CG, whether CG serves as a risk factor for anxiety disorders, or whether they are bidirectionally related. It may also be the case that certain underlying traits elevate individual risk of developing both CG and anxiety disorders. For instance, anxiety sensitivity (i.e., the fear of somatic sensations) is a transdiagnostic vulnerability trait that is an established risk factor for the development of multiple anxiety disorders [40]. There is preliminary evidence that anxiety sensitivity is also a risk factor underlying the development of CG, with studies demonstrating elevated anxiety sensitivity among bereaved adults with CG compared to bereaved adults without CG [41], in addition to an association between elevated anxiety sensitivity and worse outcomes among adults with CG [42]. Similarly, neuroticism (i.e., the tendency to experience frequent and intense negative emotions in response to stress) is another vulnerability trait underlying multiple anxiety and related disorders [43] that has also been shown to be elevated in adults with CG compared to bereaved controls [44]. As of now, we have evidence that anxiety complicates the natural grieving process, but can only speculate as to the potential mechanisms of the association between anxiety and these loss-adjustment difficulties. Overall, more research is needed to understand if and how anxiety serves as a risk factor for complicated grieving processes.

Attachment Anxiety and Bereavement

A discussion of anxiety in the context of bereavement would not be complete without a brief overview of the relationship between attachment-related anxiety and bereavement. According to attachment theory, anxiety is a natural response to separation from an attachment figure; in particular, the death of an attachment figure triggers disbelief, confusion, and disorientation and activates searching behaviors that represent an attempt to reestablish ties with the deceased [45]. For most individuals, this period of acute distress and searching behaviors eventually subside as the permanence of the loss is acknowledged and integrated into the bereaved individual's life. However, attachment theorists posit that individuals with anxious attachment styles, or a trait-like tendency to experience more uncer-

tainty about the availability of attachment figures, are prone to chronic grief patterns due to persistent searching behaviors and greater difficulty "letting go" of the attachment [46].

Indeed, there is recent research to suggest that attachment anxiety is associated with difficulty adjusting to loss. For instance, studies have found an association between attachment anxiety and prolonged grief symptomatology, as well as worse physical and mental health symptoms following a loss [47]. Maccallum and Bryant [48] recently conducted a study in which bereaved individuals were classified as having either no psychological symptoms, depression, or comorbid depression and prolonged grief; they found that attachment anxiety predicted class membership in the comorbid group, suggesting that attachment anxiety may be specifically related to complicated or prolonged grief reactions, rather than all symptoms of distress post-loss. Boelen and van den Bout [49] found that anxious avoidance, defined as avoiding confrontation with the reality of the loss, mediated the association between attachment anxiety and CG symptoms among bereaved individuals.

Separation anxiety, characterized by intense fear of becoming separated from a primary attachment figure, is often considered to be a symptom of anxious insecure attachment [50]. Studies have also shown that bereaved adults with CG are more likely to have comorbid separation anxiety disorder (SEPAD) [17] compared to bereaved adults without CG [51]. Clinical levels of SEPAD symptoms were also reported in approximately 70% of a sample of 151 adults with CG, with those individuals reporting clinical levels of SEPAD symptoms also reporting higher CG symptom severity and higher levels of grief-related avoidance compared to those who did not meet the threshold for probable SEPAD [52].

Future Directions

Overall, research has established that anxiety symptoms and disorders are prevalent in bereaved populations. However, less is known about the mechanisms or risk factors of anxiety during bereavement, as well as its distinct presentations, course, and appropriate treatment.

More work is needed to understand the mechanisms underlying anxiety symptoms and disorders in bereavement. Based on existing research, current known risk factors include poorer mental health prior to the loss, negative beliefs and cognitions associated with grief and the loss, and loss-related variables such as type of death, degree of forewarning, and relationship to the deceased. Expanding our knowledge of risk factors will contribute to more efficient and/or targeted interventions. In particular, identifying more targetable mechanisms of anxiety in bereavement, such as grief-related cognitions and beliefs, can help guide clinical intervention.

In addition, understanding whether there are distinct risk factors for the development of different anxiety and related disorders (e.g., GAD, PD, PTSD) among the

bereaved is an important area for future study. One hypothesis is that the death of a loved one is a major stressor that triggers the onset of any disorder for which an individual already has a predisposition. However, it seems to be the case that disorders such as GAD, PD, and PTSD are much more common among bereaved individuals than other anxiety disorders. This pattern suggests that there may be loss-specific factors that lead to the development of certain anxiety and related disorders and not others. For example, unexpected or particularly traumatic deaths may be more likely to trigger traumatic stress reactions over other anxiety-related symptoms. More work is needed to determine other loss-specific or circumstantial factors (e.g., intensive caregiving prior to the loss, social isolation following the loss, etc.) that may trigger certain anxiety symptoms over others. If distinct triggers do indeed exist, this type of work could lead to the identification of targetable mechanisms not only of anxiety symptoms in general but also of distinct anxiety profiles among the bereaved.

In addition to developing a more in-depth understanding of the development of anxiety symptomatology during the bereavement period, understanding how preexisting anxiety conditions, anxious attachment styles, and anxiety symptoms and disorders that develop following bereavement may put people at risk for long-term distress and impairment is an area worthy of further investigation. More longitudinal research could help elucidate the course of anxiety and related symptomatology following bereavement, including the temporal relationships between anxiety symptomatology and prolonged grief reactions, worsening anxiety symptoms and disorders, and other forms of long-term distress. This work will help determine whether and at which point anxiety interventions may be the most beneficial for bereaved individuals.

There is also a need for more studies on the treatment of anxiety disorders among bereaved individuals. As mentioned earlier in this chapter, evidence-based treatments exist for some of the most common anxiety and related disorders among bereaved individuals. However, more studies are needed to determine whether these treatments need to be tailored to address the specific needs of individuals experiencing anxiety in bereavement. Bereavement is a uniquely painful and disruptive experience, and sensitivity to the specific stressors associated with this experience likely need to be incorporated into its interventions.

In sum, anxiety is a normal and expected reaction to bereavement but one that, for many individuals, may reach clinically distressing or impairing levels and lead to long-term challenges. Thus far, research has shown us that elevated anxiety symptoms and anxiety disorders are prevalent among bereaved individuals, that there are potentially targetable mechanisms of anxiety during this period (e.g., grief-related cognitions), and that anxiety following bereavement may complicate the grieving process and lead to longer-term distress and impairment. Further studies aimed at expanding our knowledge of anxiety symptoms and disorders among bereaved individuals, including an improved understanding of its triggers, risk factors, presentation, and associated complications, are warranted.

References

1. Shear MK, Skritskaya NA. Bereavement and anxiety. Curr Psychiatry Rep. 2012;14:169–75. https://doi.org/10.1007/s11920-012-0270-2.
2. Zisook S, Schneider D, Shuchter S. Anxiety and bereavement. Psychiatr Med. 1990;8:83–96.
3. Kreicbergs U, Valdismarsdóttir U, Onelöv E, Henter J-I, Steineck G. Anxiety and depression in parents 4–9 years after the loss of a child owing to a malignancy: a population-based follow-up. Psychol Med. 2004;34:1431–41. https://doi.org/10.1017/S0033291704002740.
4. Zhang Z, Shi Z, Wang L, Liu M. Post-traumatic stress disorder, anxiety and depression among the elderly: a survey of the hard-hit areas a year after the Wenchuan earthquake. Stress Health. 2012;28:61–8. https://doi.org/10.1002/smi.1403.
5. Johnson L-M, Torres C, Sykes A, Gibson DV, Baker JN. The bereavement experience of adolescents and early young adults with cancer: peer and parental loss due to death is associated with increased risk of adverse psychological outcomes. PLoS One. 2017;12:e0181024. https://doi.org/10.1371/journal.pone.0181024.
6. Dooley B, Fitzgerald A, Giollabhui NM. The risk and protective factors associated with depression and anxiety in a national sample of Irish adolescents. Ir J Psychol Med. 2015;32:93–105. https://doi.org/10.1017/ipm.2014.83.
7. Garrido MM, Prigerson HG. The end-of-life experience: modifiable predictors of caregivers' bereavement adjustment. Cancer. 2014;120:918–25. https://doi.org/10.1002/cncr.28495.
8. Brunoni AR, Nunes MA, Pinheiro AP, Lotufo PA, Benseñor IM. Bereavement and common mental disorders in middle-aged adults: results from the Brazilian longitudinal study of adult health (ELSA-Brasil). J Affect Disord. 2014;152–154:369–74. https://doi.org/10.1016/j.jad.2013.09.039.
9. Keyes KM, Pratt C, Galea S, McLaughlin KA, Koenen KC, Shear MK. The burden of loss: unexpected death of a loved one and psychiatric disorders across the life course in a national study. Am J Psychiatry. 2014;171:864–71. https://doi.org/10.1176/appi.ajp.2014.13081132.
10. Onrust SA, Cuijpers P. Mood and anxiety disorders in widowhood: a systematic review. Aging Ment Health. 2006;10:327–34. https://doi.org/10.1080/13607860600638529.
11. Jacobs S, Hansen F, Kasl S, Ostfeld A, Berkman L, Kim K. Anxiety disorders during acute bereavement: risk and risk factors. J Clin Psychiatry. 1990;51(7):269–74.
12. Zisook S, Chentsova-Dutton Y, Shuchter SR. PTSD following bereavement. Ann Clin Psychiatry. 1998;10:157–63. https://doi.org/10.1023/A:1022342028750.
13. Kristensen P, Weisæth L, Hussain A, Heir T. Prevalence of psychiatric disorders and functional impairment after loss of a family member: a longitudinal study after the 2004 Tsunami. Depress Anxiety. 2015;32:49–56.
14. Prigerson HG, Bierhals AJ, Kasl SV, Reynolds CF III. Complicated grief as a disorder distinct from bereavement-related depression and anxiety: a replication study. Am J Psychiatry. 1996;153:1484. https://doi.org/10.1176/ajp.153.11.1484.
15. Golden A-MJ, Dalgleish T. Is prolonged grief distinct from bereavement-related posttraumatic stress? Psychiatry Res. 2010;178:336–41. https://doi.org/10.1016/j.psychres.2009.08.021.
16. Boelen PA, van den Bout J, de Keijser J. Traumatic grief as a disorder distinct from bereavement-related depression and anxiety: a replication study with bereaved mental health care patients. Am J Psychiatry. 2003;160:1339–41.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Arlington: American Psychiatric Pub; 2013.
18. Kaltman S, Bonanno GA. Trauma and bereavement: examining the impact of sudden and violent deaths. J Anxiety Disord. 2003;17:131–47. https://doi.org/10.1016/S0887-6185(02)00184-6.
19. Amick-Mcmullan A, Kilpatrick DG, Resnick HS. Homicide as a risk factor for PTSD among surviving family members. Behav Modif. 1991;15:545–59. https://doi.org/10.1177/01454455910154005.
20. Dyregrov K, Nordanger D, Dyregrov A. Predictors of psychosocial distress after suicide, SIDS and accidents. Death Stud. 2003; 27. https://doi.org/10.1080/07481180302892.

21. Hays JC, Kasl S, Jacobs S. Past personal history of dysphoria, social support, and psychological distress following conjugal bereavement. J Am Geriatr Soc. 1994;42:712–8. https://doi.org/10.1111/j.1532-5415.1994.tb06529.x.

22. Onrust S, Cuijpers P, Smit F, Bohlmeijer E. Predictors of psychological adjustment after bereavement. Int Psychogeriatr. 2007;19:921–34. https://doi.org/10.1017/S1041610206004248.

23. Chen J, Bierhals A, Prigerson HG, Kasl S, Mazure C, Jacobs S. Gender differences in the effects of bereavement-related psychological distress in health outcomes. Psychol Med. 1999;29:367–80.

24. Boelen PA, van den Bout J, van den Hout MA. The role of cognitive variables in psychological functioning after the death of a first degree relative. Behav Res Ther. 2003;41:1123–36. https://doi.org/10.1016/S0005-7967(02)00259-0.

25. He L, Yu W, Hu P, Xu W, Yan Y, Wang J. Predictive value of negative cognitive variables on emotional problems after bereavement. Chin J Clin Psych. 2014;22:605–9.

26. Mitchell AM, Sakraida TJ, Kim Y, Bullian L, Chiappetta L. Depression, anxiety and quality of life in suicide survivors: a comparison of close and distant relationships. Arch Psychiatr Nurs. 2009;23:2–10. https://doi.org/10.1016/j.apnu.2008.02.007.

27. Erlangsen A, Runeson B, Bolton JM, Wilcox HC, Forman JL, Krogh J, et al. Association between spousal suicide and mental, physical, and social health outcomes: a longitudinal and nationwide register-based study. JAMA Psychiat. 2017;74:456–64. https://doi.org/10.1001/jamapsychiatry.2017.0226.

28. Cerel J, Fristad MA, Weller EB, Weller RA. Suicide-bereaved children and adolescents: a controlled longitudinal examination. J Am Acad Child Adolesc Psychiatry. 1999;38:672–9. https://doi.org/10.1097/00004583-199906000-00013.

29. Valdimarsdóttir U, Helgason ÁR, Fürst C-J, Adolfsson J, Steineck G. Awareness of husband's impending death from cancer and long-term anxiety in widowhood: a nationwide follow-up. Palliat Med. 2004;18:432–43. https://doi.org/10.1191/0269216304pm891oa.

30. Carr D, House JS, Wortman C, Nesse R, Kessler RC. Psychological adjustment to sudden and anticipated spousal loss among older widowed persons. J Gerontol B Psychol Sci Soc Sci. 2001;56:S237–48. https://doi.org/10.1093/geronb/56.4.S237.

31. Kersting A, Brähler E, Glaesmer H, Wagner B. Prevalence of complicated grief in a representative population-based sample. J Affect Disord. 2011;131:339–43. https://doi.org/10.1016/j.jad.2010.11.032.

32. Bergman EJ, Haley WE, Small BJ. The role of grief, anxiety, and depressive symptoms in the use of bereavement services. Death Stud. 2010;34:441–58. https://doi.org/10.1080/07481181003697746.

33. Janssen HJ, Cuisinier MC, de Graauw KP, Hoogduin KA. A prospective study of risk factors predicting grief intensity following pregnancy loss. Arch Gen Psychiatry. 1997;54:56–61. https://doi.org/10.1001/archpsyc.1997.01830130062013.

34. Eisma MC, Boelen PA, Schut HA, Stroebe MS. Does worry affect adjustment to bereavement? A longitudinal investigation. Anxiety Stress Coping. 2017;30:243–52. https://doi.org/10.1080/10615806.2016.1229464.

35. Jacobson NC, Lord KA, Newman MG. Perceived emotional social support in bereaved spouses mediates the relationship between anxiety and depression. J Affect Disord. 2017;211:83–91. https://doi.org/10.1016/j.jad.2017.01.011.

36. Marques L, Bui E, LeBlanc N, Porter E, Robinaugh D, Dryman MT, et al. Complicated grief symptoms in anxiety disorders: prevalence and associated impairment. Depress Anxiety. 2013;30:1211–6. https://doi.org/10.1002/da.22093.

37. Bui E, LeBlanc NJ, Morris LK, Marques L, Shear MK, Simon NM. Panic-agoraphobic spectrum symptoms in complicated grief. Psychiatry Res. 2013;209:118–20. https://doi.org/10.1016/j.psychres.2013.03.033.

38. Bui E, Horenstein A, Shah R, Skritskaya NA, Mauro C, Wang Y, et al. Grief-related panic symptoms in complicated grief. J Affect Disord. 2015;170:213–6. https://doi.org/10.1016/j.jad.2014.08.028.

39. Sung SC, Dryman MT, Marks E, Shear MK, Ghesquiere A, Fava M, et al. Complicated grief among individuals with major depression: prevalence, comorbidity, and associated features. J Affect Disord. 2011;134:453–8. https://doi.org/10.1016/j.jad.2011.05.017.
40. Naragon-Gainey K. Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. Psychol Bull. 2010;136:128. https://doi.org/10.1037/a0018055.
41. Robinaugh DJ, McNally RJ, LeBlanc NJ, Pentel KZ, Schwarz NR, Shah RM, et al. Anxiety sensitivity in bereaved adults with and without complicated grief. J Nerv Ment Dis. 2014;202:620. https://doi.org/10.1097/NMD.0000000000000171.
42. Baker AW, Goetter EM, Bui E, Shah R, Charney ME, Mauro C, et al. The influence of anxiety sensitivity on a wish to die in complicated grief. J Nerv Ment Dis. 2016;204:314.
43. Barlow DH, Sauer-Zavala S, Carl JR, Bullis JR, Ellard KK. The nature, diagnosis, and treatment of neuroticism: back to the future. Clin Psychol Sci. 2014;2:344–65.
44. Goetter E, Bui E, Horenstein A, Baker AW, Hoeppner S, Charney M, et al. Five-factor model in bereaved adults with and without complicated grief. Death Stud. 2019;43:2014–209.
45. Bowlby J. Attachment and loss: volume 3. New York: Basic Books; 1980.
46. Field NP, Sundin EC. Attachment style in adjustment to conjugal bereavement. J Soc Pers Relat. 2001;18:347–61. https://doi.org/10.1177/0265407501183003.
47. Meier AM, Carr DR, Currier JM, Neimeyer RA. Attachment anxiety and avoidance in coping with bereavement: two studies. J Soc Clin Psychol. 2013;32:315–34. https://doi.org/10.1521/jscp.2013.32.3.315.
48. Maccallum F, Bryant RA. Prolonged grief and attachment security: a latent class analysis. Psychiatry Res. 2018;268:297–302. https://doi.org/10.1016/j.psychres.2018.07.038.
49. Boelen PA, van den Bout J. Anxious and depressive avoidance and symptoms of prolonged grief, depression, and post-traumatic stress disorder. Psychol Belg. 2010; https://doi.org/10.5334/pb-50-1-2-49.
50. Bowlby J. Attachment and loss: volume 2. New York: Basic Books; 1973.
51. Pini S, Gesi C, Abelli M, Muti M, Lari L, Cardini A, et al. The relationship between adult separation anxiety disorder and complicated grief in a cohort of 454 outpatients with mood and anxiety disorders. J Affect Disord. 2012;143:64–8. https://doi.org/10.1016/j.jad.2012.05.026.
52. Gesi C, Carmassi C, Shear KM, Schwartz T, Ghesquiere A, Khaler J, et al. Adult separation anxiety disorder in complicated grief: an exploratory study on frequency and correlates. Compr Psychiatry. 2017;72:6–12. https://doi.org/10.1016/j.comppsych.2016.09.002.

Chapter 11
Suicide in Anxiety Disorders

René M. Lento and Heidi Boland

Introduction

Suicide poses an international public health problem, with reports indicating almost one million suicide deaths worldwide each year [1]. In the United States, suicide constitutes the tenth leading cause of death, with estimates of nearly 45,000 suicides annually [2, 3]. Further, suicide is one of only leading causes of death that has been steadily increasing over the past decade [4]. Suicidal thoughts and attempts are also a cause for international and domestic concern [5, 6]. In 2013, in the United States alone, 9.3 million adults reported past-year suicidal ideation, and 1.3 million endorsed having attempted suicide [7].

Historically, the association between suicide and mood disorders has often overshadowed consideration of anxiety disorders when assessing for suicide risk. Yet, several notable studies observed the presence of acute anxiety symptoms in the days and hours preceding near-lethal suicide attempts [8] and fatal suicides [9]. Moreover, data from the National Comorbidity Survey Replication showed anxiety disorders[1] to be the most common class of disorders among people with suicide-related behaviors [10]. Lifetime suicide attempt estimates among people who met criteria for an

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[1] The National Comorbidity Survey Replication used anxiety disorder criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). At that time, the DSM-IV included posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) as anxiety disorders. PTSD and OCD are no longer classified as anxiety disorders in the DSM-5.

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anxiety disorder ranged from approximately 42.0% for specific phobia and social anxiety disorder (SAD) to 6.8% for agoraphobia without panic disorder. Over the past two decades, anxiety disorder subtypes and symptoms have been empirically evaluated as unique risk factors for suicidal ideation [6, 11, 12], attempts [6, 11, 13, 14], and deaths [15, 16]. Anxiety disorders and anxious states characterized by agitation or a desire to escape are also commonly featured among lists of warning signs and risk factors published by national organizations [17, 18]. Thus, substantial empirical and clinical interest has developed regarding anxiety disorders' role in understanding, assessing, and treating suicide-related behaviors.

In this chapter we will review the evidence linking primary and comorbid anxiety disorders to suicide-related behaviors and deaths. We will then present considerations for the assessment and treatment of suicide risk within this population and conclude with suggestions for future research.

Empirical Overview and Conceptualization

Research on anxiety disorders as potentially independent and clinically useful risk factors for suicide-related behaviors initially produced equivocal results. For instance, among anxiety disorders, panic disorder (PD) has been one of most thoroughly researched regarding suicide-related behaviors. Early studies indicated that, after accounting for major depression (MDD) and substance use disorders (SUDs), 12% of people with panic attacks and 20% of participants with a history of PD had a lifetime suicide attempt [19]. PD has also been associated with past-year suicidal ideation and attempts, even after controlling for psychiatric comorbidity [13, 20–23]. Other large-scale prevalence studies, however, noted evidence for an association between specific phobia and suicide attempts, but not for PD [23]. Similarly, after controlling for demographic variables and comorbidity, Cougle and colleagues [24] found generalized anxiety disorder (GAD), SAD, and PTSD, but not PD to be predictive of suicide attempts (though PD was still predictive of suicidal ideation). Investigations into other, anxiety diagnoses have been equally discrepant, with some studies supporting and others contradicting an independent association of GAD [11, 22, 23], OCD [11, 25], SAD [11, 24], specific phobia [23, 26], PTSD [13, 24, 26], or agoraphobia [11, 23] with suicide ideation and/or attempts.

Meta-analyses attempting to clarify the relationships among anxiety disorders and suicide outcomes have concluded that trait-like anxiety constructs and specific anxiety disorders *do* have a unique, though small, association with suicidal ideation and attempts. One meta-analysis of 42 studies through August 2011 found patients with anxiety diagnoses to be nearly three times more likely to manifest suicidal ideation and over twice as likely to have suicide attempts when compared to patients who did not have anxiety diagnoses [27]. The authors also found anxiety patients of all diagnoses to be three times more likely to die by suicide. However, the substantial heterogeneity among study methodologies (e.g., inconsistencies in diagnostic criteria used and inclusion of confounding variables) limited the quality of this evidence [27, 28].

A more recent meta-analysis by Bentley and colleagues [29] incorporated 65 studies conducted through 2014, with a focus on anxiety-specific longitudinal predictors of suicide outcomes. Odds ratios (OR) demonstrated that anxiety, both when measured as anxiety symptoms and as separate diagnoses, was a statistically significant but weak (OR ≤ 2.25) longitudinal predictor of suicidal ideation and attempts. Moreover, *none* of the anxiety constructs or diagnoses were found to significantly predict suicide deaths. Therefore, an anxiety diagnosis alone may provide limited assistance for clinical decision-making about suicide, though the same would likely be true for any suicide risk factor considered in isolation.

More impactful from a clinical standpoint appears to be the *added* risk when anxiety disorders and acute anxiety symptoms co-occur with other psychiatric conditions, including mood disorders [30–34], schizophrenia [28], SUDs [35], and personality disorders [13, 36]. Particularly compelling have been findings of additive risk for patients with comorbid mood diagnoses. Comprehensive prevalence studies have demonstrated that on their own, both classes of disorders are comparably associated with the onset of suicidal thoughts [32, 37]; however, the comorbid presence of both a mood and an anxiety disorder is related to a higher likelihood of suicide attempts compared to either condition alone [32]. For example, in comparing individuals with PD to those with comorbid PD and depression, Diaconu and Turecki [32] found the pure PD group to have a significantly lower number of suicide attempts (7% suicide attempt rate) compared to the comorbid group (20% suicide attempt rate). Furthermore, even after controlling for demographics and SUDs, Pfeiffer and colleagues [30] demonstrated increased odds of suicide among depressed patients with comorbid PD or GAD.

Acute anxiety presentations, particularly when they occur in the context of a mood disorder, may provide even greater clinical utility for short-term assessment of suicide risk. In a series of studies of patients with mood disorders, Fawcett and colleagues [9, 38, 39] consistently found severe panic attacks, worry, and agitation to be acute precursors to suicide. In one sample of 954 psychiatric patients with mood disorder diagnoses, panic attacks and psychic anxiety were among six features associated with suicide within the first year of follow-up [9]. Additionally, in their study of suicide death, Pfeiffer and colleagues [30] found that among depressed US Veterans, prescription of daytime doses of antianxiety medication (benzodiazepines or buspirone) was a stronger predictor of suicide than were comorbid anxiety diagnoses. Odd ratios were further elevated among those with high dose prescriptions. Accordingly, the authors noted that the severity of anxiety symptoms may in fact be more indicative of suicide risk than the diagnosis itself [30]. Recent studies have also demonstrated increased rates of suicidal ideation and attempts among patients with anxious depression compared to depression alone [31, 40] and among persons with MDD who experience anxiety attacks (i.e., "sudden attack of fear or intense anxiety") in non-life-threatening situations [33].

Nock and colleagues [41] expounded upon the connection between co-occurring mood and anxiety conditions and suicide risk. Their analyses revealed that depression diagnoses predicted suicidal ideation but did not predict progression to planning or attempts. Rather, the only disorders that predicted which persons with ideation would proceed to action were those characterized by anxiety and poor

impulse control. Hence, the authors hypothesized that while distinctive aspects of depression, such as hopelessness, may create the conditions for suicidal ideation, the impetus to escape that is inherent in anxiety disorders may foster the progression to suicidal actions [41]. A study of characteristic differences between suicide attempters who had mood disorders alone, compared to those with a comorbid mood disorder and PTSD, found support for this hypothesis [42]. Specifically, patients in the comorbid group were more likely to report erratic behavior at the time of their attempt, including being under the influence of alcohol and acting impulsively [42].

Nock and colleagues' explanation is also consistent with the "ideation-to-action" framework of suicide, which highlights the categorical differences among those who have suicidal thoughts compared to those who go on to attempt or die from suicide [43]. Examples of ideation-to-action models include the interpersonal theory (IPTS [44]), three-step theory (3ST) [45], and the integrated motivation-volitional (IVM) model of suicidal behavior [46]. These theories emphasize identifying whether a predictor *specifically* addresses suicide ideation, suicide attempts, or both, rather than assuming that a predictor for one type of suicidal presentation will automatically encompass the other [43]. For instance, in the IPTS, thwarted belongingness (e.g., disconnection from others, absence of reciprocal care) and perceived burdensomeness (e.g., belief that one is a liability, self-hatred) are specifically linked to the genesis of suicidal thoughts, but, on their own, are not believed to instigate suicide attempts. Instead, acquired capability (e.g., reduced pain sensitivity, fearlessness of death) is presented as a critical element that moves someone with ideation to attempt [44, 47]. Alternatively, 3ST postulates that (1) *moderate* suicidal ideation arises from the combination of pain and hopelessness, (2) *strong* suicidal ideation occurs when an individual's pain exceed his/her sense of meaningful connection to others, and (3) suicide attempts transpire when the individual with strong ideation further possesses the "capability" to attempt (e.g., *dispositional* pain insensitivity, *acquired* habituation to pain or fear, or *practical* access to lethal means) [45]. In turn, IMV proposes that chronic or acute stressors lead to defeat or humiliation appraisals, followed by feelings of entrapment (e.g., suicide seen as solution to life circumstances), then to suicidal ideation and intention, and finally to suicidal behavior [46]. Transitions from one stage to the next are facilitated or obstructed by numerous stage-specific moderators (e.g., memory biases, social support, access to means).

An alternative explanation for the impact of comorbid anxiety on suicidal behavior is that the *cumulative* impact of multiple psychiatric conditions leads to an intolerable buildup of emotional or psychological pain and overwhelming cognitions, resulting in a suicidal crisis and actions [48, 49]. Studies have commented on the tendency for rates of suicidal ideation and behavior to increase in proportion to the number of disorders identified [21]. Also consistent with this notion of enhanced psychological pain is that individuals with anxious depression, compared to depression alone, have been found to exhibit more severe and entrenched depressive symptomology (i.e., younger age of onset, longer duration of depression, higher likelihood of depressive reoccurrence) and to report lower quality-of-life scores [31, 40].

A final emerging area of interest involves the construct of anxiety sensitivity (AS). AS is considered distinct from trait anxiety and is defined as the fear of anxiety-related sensations [50, 51]. AS is further divided into three subgroups: *cognitive* (e.g., concern that one is going crazy or losing control), *physical*, (e.g., concern that anxiety-related physiological symptoms indicate an impending health problem such as having a heart attack or passing out), and *social* (e.g., fear of social rejection or embarrassment due to observable anxiety symptoms like trembling). Each AS subgroup has been linked to specific anxiety and mood diagnoses. Logistic regression models have found higher levels of cognitive AS concerns to significantly predict increased odds of meeting diagnostic criteria for GAD, PTSD, and MDD [52]. In turn, high levels of physical AS were found to predict increased odds for PD and specific phobia diagnoses, while high levels of social AS were predictive of greater odds for meeting SAD diagnostic criteria [52]. Moreover, studies have identified overall AS and AS subgroups as transdiagnostic risk factors for suicidal thoughts and behaviors among a range of patient populations [53–56]. In a recent meta-analysis, all AS subgroups were associated with suicidal ideation and "suicide risk," defined by the authors as a combination of suicidal ideation, past suicide attempts, and intent to engage in future attempts [51]. AS cognitive concerns have accumulated the most consistent evidence as a suicide risk factor, especially in context of depression [52, 55, 57]. One study of firefighters, though, found a comparatively strong interaction between depression symptoms and AS social concerns in predicting suicide risk [57]. While further research is needed to explain this finding, the researchers hypothesized that manifestations of anxiety may exacerbate distress via shame or social isolation due to the high value of stoicism among firefighters [57]. This risk combination of depression and either cognitive or social AS may in turn be potentiated by the presence of *low* physical AS, because, consistent with IPTS and 3ST models previously discussed, low levels of fear about physical harm may facilitate an acquired capability to engage in suicidal behaviors [44, 51, 54].

Assessment

Pre-assessment Considerations

Proficiency in suicide risk assessment is a fundamental expectation held for mental health providers of all disciplines and who serve all patient populations [58, 59]. While predicting precisely who will die by suicide is an impossible task [60], identifying patients at elevated risk and formulating an appropriate risk management plan is achievable [61, 62]. Still, conducting a thorough risk evaluation while balancing real-world time restraints and meeting documentation standards can be an understandably daunting undertaking for clinicians of any skill level. Thus, like preparing for any situation that has high stakes but low frequency of occurrence, conducting a thoughtful and effective suicide risk assessment benefits from adequate

preparation and overlearning. To this end, providers working with any patient population can do a great deal to boost confidence and competence prior to ever meeting with a suicidal individual.

First, screening measures should be incorporated as a routine part of intake evaluations and ongoing care [59, 61, 63]. Use of screening measures is exceptionally useful for alerting clinicians to possible high-risk situations directly prior to a session, so that a more extensive risk evaluation can be conducted early in the clinical visit. To achieve this end, it is important to review these screening forms in nearly real time. In addition, patients may feel more comfortable disclosing suicidal ideation on a questionnaire [64]. Second, it is recommended that providers have electronic and/or hard-copy assessment and crisis management forms that are immediately accessible should the need for a more detailed risk assessment arise. Comprehensive evidence-based tools are readily available to providers online through forums such as the Zero Suicide [65] initiative and the US Department of Veterans Affairs [66]. Third, it is important that providers clearly understand the emergency procedures for their organization or practice. While inpatient hospitalization should only be used when the patient is deemed truly incapable of keeping himself/herself safe and a less restrictive care settings is not available [67], practicing the steps for contacting emergency support, arranging transport, and documenting actions taken will allow for a calmer and more effective experience for both the provider and the patient. Being able to walk patients through what they can expect and how the referring provider intends to coordinate with a higher level of care can also help to alleviate anxiety for patients and their loved ones, who are already in a vulnerable state.

Fourth, even for suicidology experts, consultation is critical for enabling providers to act and feel competent when working with high-risk patients [68]. As with the other recommendations, it is helpful to identify appropriate colleagues, supervisors, or organizations in advance. The VA Suicide Risk Management Consultation Program [69] is one such organization that offers a free consultation service for all community providers serving veterans at risk for suicide. Finally, clear, accurate, and timely documentation is essential for fostering good coordination of care; it can also provide peace of mind for providers with liability concerns [58]. Have prepared note templates that include documentation of the following components (which will be discussed in further detail below): suicidal ideation, plans, urges, and intent, access to potentially lethal means, recent substance use patterns, social support and connection, and other notable risk and protective factors, as well as any therapeutic actions taken (e.g., coaching of family members, means restriction, safety planning), plans for ongoing monitoring, and engagement in consultation.

Process Considerations

Providers can also benefit from reflecting on their own attitudes, as addressing suicide risk is often a source of anxiety for patients and clinicians alike. Suicide attempt survivors seeking treatment frequently report experiencing invalidation at a time

when nonjudgmental support and collaborative problem-solving are most needed [70]. Fear of stigma, overreaction, or repercussions on work and family life can additionally prevent help seeking and inhibit disclosure of suicidal ideation [71, 72]. In one study of 76 patients who died by suicide while hospitalized or immediately following discharge, 78% denied suicidal ideation at their last communication with providers [15]. While screening measures that do not rely on self-report are needed [73], there is also an onus on mental health providers to establish an environment where suicidal patients feel understood and accepted [61].

Accordingly, it is important to inquire about suicidal thoughts, plans, and urges directly and unabashedly [74], rather than in ways that could be construed as unwelcome (i.e., "sorry, I have to ask all new intakes this"), dismissive (i.e., "you're not having any suicidal thoughts, right?"), or that otherwise imply that the provider is uncomfortable with disclosure of suicide risk (often communicated nonverbally or through failure of the therapist to ask). A more productive approach is to ask calmly and candidly if the person is thinking about killing themselves, which may include normalizing the patient's experience in the context of current stressors and symptoms (i.e., "Many people who experience severe panic attacks like you described also report thoughts of death or of killing themselves. Have you had any thoughts like this? How about in the past?"). Furthermore, it is helpful for providers to be aware, and to communicate to patients, that suicidal ambivalence (i.e., simultaneously desiring to live and desiring to die or escape from pain) is a common experience [75, 76]) and that therapy is the appropriate place to safely discuss this internal struggle [61, 77].

Content Considerations

Although not an exhaustive list, the following comprise key content areas to inquire about during a suicide risk assessment. Given the high rate of nondisclosure among suicidal patients [72] and the potential for more impulsive escape behaviors among individuals with anxiety disorders [41], there may be value in asking some questions about lethal means [42, 78], substance use [35, 42, 71], and social support [79] regardless of suicidal ideation endorsement.

Suicidal Ideation, Plans, and Intent Inquiry about suicidal ideation can stem from follow-up on an endorsed screening item or by directly asking early in the session. Comments about hopelessness [80], urges to escape from stressors/symptoms [48], elevation in acute anxiety symptoms [9, 15], or intensified cognitive AS concerns [50] that arise during a session should also trigger asking about new onset or worsening of suicidal thoughts. Among patients who endorse suicidal thoughts, a logical next step is to inquire if the person has considered how they would carry out an attempt and his/her intention to act on these thoughts. Asking about ideation, plans, and intent will not increase a patient's suicide risk [81]. However, of note, among approximately 1.3 million US adults who endorsed a past-year suicide

attempt, 200,000 of these individuals denied having made a suicide plan [2]. Therefore, even in the absence of a plan or current intent, assessment of lethal means and variables that facilitate impulsive behavior (e.g., substance use) remains important.

Lethal Means Firearms remain the most common method of suicide in the United States [2]. Accordingly, suicide prevention advocates and researchers encourage clinical inquiry about access to firearms, as well as education of safe storage practices (i.e., in a locked safe with ammunition stored separately) as a public health intervention [78, 82]. In addition, poisoning, which is considered a nonviolent method, accounts for 20% of US suicide deaths among persons diagnosed with a mental health condition [2]. Suicide among both males and females with anxiety disorders have been associated with an increased likelihood of nonviolent suicide methods [16]. Consequently, comprehensive assessment of both violent and nonviolent means appears to be particularly relevant when conducting risk evaluations with anxiety disorder patients.

Substance Use Heavy episodic alcohol use (i.e., defined in studies as 8 or more drinks per week for women and 15 or more drinks per week for men or self-defined "binges" per patient report) and other substance use are commonly reported at the time of suicide attempts even among individuals who do not meet criteria for a SUD [71, 83]. Some research suggests that depressed persons with comorbid anxiety disorders may be more likely to be intoxicated at the time of an attempt [42], and use of substances to self-medicate anxiety symptoms has been linked to higher incidence of suicide attempts [35]. Researchers have also hypothesized that the lowered inhibitions facilitated by some antianxiety medications may in turn contribute to the increased odds of suicide death among individuals with mood disorders [30].

Social Support and Connection Social connection and interpersonal factors (e.g., perceived burdensomeness, thwarted belongness) are prominent features of theoretical models of suicide [44, 45] and frequently serve as a significant risk or protective factors for suicide. Especially in elderly populations, anxiety disorders [84] and anxious depression (compared to depression alone, [85]) have been associated with suicidal ideation and more impairments in perceived social support.

Other Risk Factors, Protective Factors, and "Drivers" Numerous other transdiagnostic risk factors (e.g., attempt history, unemployment, family history of suicide, chronic pain, insomnia [86]) and protective factors (e.g., spiritual faith, family connectedness, problem-solving skills [87]) have been identified and may be clinically useful when considered in aggregate. However, individuals with suicidal ideation are a heterogenous group and there is no one-size-fits-all approach to delineate how risk factors will manifest into action [88]. More constructive from a clinical standpoint may be to understand the *drivers* or the person-specific factors that a patient states are underlying his/her desire to die by suicide [89]. Some individuals may attribute this desire to the severity of their anxiety symptoms, in which case direct treatment of the anxiety disorder may alleviate ideation. Another

person may experience equally severe anxiety symptoms yet ascribe their suicidal ideation to a secondary factor like loneliness, in which case a range of alternative interventions may be effective to directly target the source of the ideation. Assessment measures that include both quantitative and qualitative items, such as the Suicide Status Form (SSF, [90]), can be helpful tools for facilitating these discussions. Likewise, inquiring about a patient's *reasons for dying and reasons for living* [91, 92] can provide insight into personally significant drivers, as well as the protective factors considered most relevant to the patient. Knowledge of both sides contributes to the end goal of generating an effective and person-centered risk management plan.

Treatment

Treatment for suicide risk typically takes two forms. The first encompasses strategies to provide short-term stabilization and crisis management. The second includes interventions aiming to produce long-term reductions in suicidal ideation and behaviors and/or eradication of underlying drivers.

Crisis Management

Crisis management occurs in tandem with identification of elevated suicide risk. In the past, use of "no-suicide contracts" or "contracting for safety" was commonly presented to patients as an alternative to inpatient hospitalization. However, these contracts, which elicit a promise from the patients that they will not harm themselves, have been found to be largely ineffective because they do not empower patients with skills to manage suicidal thoughts and urges [93, 94]. Instead, crisis response or safety plans [94–96] are now considered a vital component of suicide risk management [59, 61]. Safety plans entail a concrete discussion of a patient's idiosyncratic warning signs of escalating suicide risk (e.g., sleep deprivation, not returning phone calls, thought that "this would be easier if I was dead"), followed by brainstorming of coping strategies that can be used alone (e.g., go for a walk, practice breathing exercises, take very hot or cold shower), and in collaboration with others who may or may not be aware that the patient is experiencing suicidal ideation (e.g., go to a coffee shop, go to the gym, call friend for distraction). The patient also specifically identifies individuals he/she could contact for support, as well as professionals, crisis hotlines, and emergency resources. Moreover, all safety plans include a discussion of lethal means restriction (e.g., remove firearms from the home, reduce quantity of pills in medications refills, [95]). As a result, the patient leaves the session equipped with a personalized, step-by-step guide of how to remain safe during what is often a short-lived suicidal crisis. Suicidal urges usually decrease in intensity within minutes to hours and only rarely extend beyond a

day [82]. A modified version of Stanley and Brown's (2008) safety plan template is provided in Appendix; more detailed instructions are available in their safety planning treatment manual [97].

Although hospitalization has often been a standard practice in crisis management, reviews of evidenced-based interventions for suicide risk caution that no clinical trials have actually found inpatient stays to reduce future incidence of suicide attempts or deaths [98, 99]. Rather the costs of hospitalizations, financially and in terms of stigma and role disruptions, may unintentionally leave patients and their families worse off [98]. Accordingly, current guidelines recommend a stepped care approach [100] that promotes treatment of suicide risk in outpatient settings (or the least restrictive setting that is appropriate) and avoidance of hospitalization whenever possible [59, 61].

Interventions for Resolution of Suicidal Ideation

Considering the heighted risk for suicidal thoughts and behaviors among individuals with anxiety disorders and acute anxiety symptoms, researchers have often hypothesized that treatment of anxiety disorders or symptoms themselves may lead to reductions in suicide risk [11, 21, 101]. To date there has been some evidence to support that CBT for anxiety is accompanied by reductions in suicidal ideation for patients with PTSD and SAD [102]. A preliminary investigation of the Unified Protocol [103] implemented in an inpatient setting also found promising reductions in suicidal ideation, anxiety, and depression symptoms from admission to discharge [104], though these reductions were not statistically distinct from the treatment-as-usual comparison. Another recent study of patients with co-occurring suicidal ideation and anxiety symptoms found a single-session computerized intervention called the cognitive anxiety sensitivity treatment (CAST) to demonstrate reductions in suicidal ideation at a 4-month follow-up [105]. In addition, the authors found a chain mediation effect, linking posttreatment AS to 1-month follow-up cognitive anxiety symptoms and linking cognitive anxiety symptoms to decreased suicidal ideation.

Pharmacological options have also shown some efficacy in reducing suicidal ideation and urges, though these have primarily been studied in the context of mood disorder populations [106]. Notable among these interventions, however, is emerging interest in ketamine, typically used as an anesthetic or for postoperative pain relief. Ketamine is a *N*-methyl-D-aspartate (NMDA) receptor antagonist that has been found to reduce suicidal ideation in part through improvements in depression and anxiety [107]. Ketamine trials have demonstrated reductions in suicidal ideation and anxiety symptoms within hours of administration [108, 109], though further research is needed to establish safety and long-term effectiveness [106].

An alternative approach that has received a great deal of support is to directly target and treat suicidal ideation and behaviors with transdiagnostic outpatient psychotherapy protocols [98, 99]. The best studied among these include dialectical

behavioral therapy (DBT, [110]), cognitive therapy for suicide prevention (CT-SP, [111, 112]), and the collaborative assessment and management of suicidology (CAMS, [113]). All three have demonstrated efficacy in reduced ideation or attempts when compared to treatment as usual or individual and group supportive therapy [111, 113–117]. DBT currently has the strongest empirical support for reducing suicidal ideation and attempts in adults and adolescents (e.g., [115, 118–121]), though of note, DBT trials have predominantly featured female samples [122]. Broadly speaking, these psychotherapy approaches focus on identifying the drivers or functional roles that suicidal thoughts and behaviors serve for the patient, as well as the underlying skills deficits and/or core beliefs that need to be addressed for the patient to reestablish a life worth living.

Conclusions and Future Directions

Individuals with anxiety disorders are at heighted risk for suicidal ideation and behaviors [10, 11], particularly when anxiety symptoms occur in the context of comorbid mood disorders [30]. However, more longitudinal studies on the association between anxiety and suicide deaths are needed, as well as studies that more explicitly address the role of *acute* anxiety presentations in the days and hours preceding suicide attempts [29]. Current explanations for the association between anxiety and suicidal behaviors include the hypothesis that depressive symptoms predispose individuals for suicidal ideation, but anxiety symptoms incite an urge to escape that facilitates attempts [41]. Alternatively, anxiety symptoms may contribute to an intolerable cumulation of psychological pain or cognitive distress [48, 51]. It will be important for future research to reconcile these findings with theoretical models of suicide, especially as the field progresses with testing of ideation-to-action theories [90].

Moreover, routine assessment of suicidal ideation and behaviors remains imperative among anxiety disorder patients and should always be conducted in an empathic and patient-centered manner. Inquiring about access to possible lethal means (violent and non-violent) and use of substances to manage anxiety symptoms is highly recommended even among patients who do not endorse imminent plans or intent [16, 79]. Crisis management of patients identified to be at elevated risk is encouraged to occur in an outpatient setting, when at all possible, and to incorporate empowering, problem-solving interventions such as safety plans instead of no-suicide contracts [96]. Additional studies that clarify if and how suicidal behaviors manifest differently in patients with anxiety disorders compared to other diagnostic presentations are necessary to inform more tailored crisis management recommendations.

Finally, although there is some evidence for indirectly treating suicidal ideation through therapies designed to alleviate anxiety disorder symptoms [104], current treatment guidelines support the use of transdiagnostic psychotherapies that focus directly on addressing suicidal thoughts and behaviors [62]. Additional clinical tri-

als on the efficacy of suicide-focused interventions, as well as emerging computer-based [107] and medication [109] options to prevent suicide attempts and deaths, will be essential for shaping clinical practice in the years to come.

Appendix

Safety Plan

Step 1: Warning signs:

1. _____
2. _____
3. _____

Step 2: Internal coping strategies – Things I can do first to take my mind off my problems without contacting another person:

1. _____
2. _____
3. _____

Step 3: People and social settings that provide distraction:

1. Name_____ Phone_____
2. Name_____ Phone_____
3. Place_____ 4. Place _____

Step 4: People whom I can ask for support:

1. Name_____ Phone_____
2. Name_____ Phone_____
3. Name_____ Phone_____

Step 5: Professionals or agencies I can contact during a crisis:

1. Clinician Name: _____ Phone: _____
   Clinician Pager or Emergency Contact #_____
2. Clinician Name_____ Phone_____
   Clinician Pager or Emergency Contact #_____
3. Local Urgent Care Services _____
   Urgent Care Services Address_____
   Urgent Care Services Phone _____
4. Mental Health Crisis Hotline: 1-800-273-TALK (8255)
5. Online chat: www.suicidepreventionlifeline.org

Step 6: Making the environment safe:

1. _____
2. _____

Adapted from Stanley and Brown [97]

References

1. WHO. Public health action for the prevention of suicide. 2012. Retrieved January 11, 2019, from https://www.who.int/mental_health/publications/prevention_suicide_2012/en/
2. CDC. CDC vital signs. 2018a, November 27. Retrieved January 11, 2019, from https://www.cdc.gov/vitalsigns/suicide/index.html
3. CDC. CDC WISQARS. 2018b, December 3. Retrieved January 11, 2019, from https://www.cdc.gov/injury/wisqars/index.html

4. Stone DM. Vital signs: trends in state suicide rates — United States, 1999–2016 and circumstances contributing to suicide — 27 states, 2015. MMWR Morb Mortal Wkly Rep. 2018;67:617–24.

5. Olfson M, Blanco C, Wall M, Liu S-M, Saha TD, Pickering RP, Grant BF. National trends in suicide attempts among adults in the United States. JAMA Psychiat. 2017;74(11):1095–103.

6. Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Br J Psychiatry J Ment Sci. 2008;192(2):98–105.

7. SAMHSA. Results from the 2013 national survey on drug use and health: mental health findings, *HHS Publication No. (SMA) 14-4887*; 2014. p. 142.

8. Hall RC, Platt DE, Hall RC. Suicide risk assessment: a review of risk factors for suicide in 100 patients who made severe suicide attempts. Evaluation of suicide risk in a time of managed care. Psychosomatics. 1999;40(1):18–27.

9. Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R. Time-related predictors of suicide in major affective disorder. Am J Psychiatry. 1990;147(9):1189–94.

10. Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990–1992 to 2001–2003. JAMA. 2005;293(20):2487–95.

11. Sareen J, Cox BJ, Afifi TO, de Graaf R, Asmundson GJG, ten Have M, Stein MB. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. Arch Gen Psychiatry. 2005;62(11):1249–57.

12. O'Neil Rodriguez KA, Kendall PC. Suicidal ideation in anxiety-disordered youth: identifying predictors of risk. J Clin Child Adolesc Psychol. 2014;43(1):51–62.

13. Nepon J, Belik S-L, Bolton J, Sareen J. The relationship between anxiety disorders and suicide attempts: findings from the National Epidemiologic Survey on alcohol and related conditions. Depress Anxiety. 2010;27(9):791–8.

14. Park S, Lee Y, Youn T, Kim BS, Park JI, Kim H, et al. Association between level of suicide risk, characteristics of suicide attempts, and mental disorders among suicide attempters. BMC Public Health. 2018;18(1):477.

15. Busch KA, Fawcett J, Jacobs DG. Clinical correlates of inpatient suicide. J Clin Psychiatry. 2003;64(1):14–9.

16. McGirr A, Séguin M, Renaud J, Benkelfat C, Alda M, Turecki G. Gender and risk factors for suicide: evidence for heterogeneity in predisposing mechanisms in a psychological autopsy study. J Clin Psychiatry. 2006;67(10):1612–7.

17. American Association of Suicidology. Warning signs & risk factors. 2019. Retrieved January 11, 2019, from http://www.suicidology.org/ncpys/warning-signs-risk-factors

18. American Foundation for Suicide Prevention. Risk factors and warning signs. 2016. Retrieved January 11, 2019, from https://afsp.org/about-suicide/risk-factors-and-warning-signs/

19. Weissman MM, Klerman GL, Markowitz JS, Ouellette R. Suicidal ideation and suicide attempts in PD and attacks. N Engl J Med. 1989;321(18):1209–14.

20. Goodwin RD, Roy-Byrne P. Panic and suicidal ideation and suicide attempts: results from the National Comorbidity Survey. Depress Anxiety. 2006;23(3):124–32.

21. Boden JM, Fergusson DM, Horwood LJ. Anxiety disorders and suicidal behaviours in adolescence and young adulthood: findings from a longitudinal study. Psychol Med. 2007;37(3):431–40.

22. Goldston DB, Daniel SS, Erkanli A, Reboussin BA, Mayfield A, Frazier PH, Treadway SL. Psychiatric diagnoses as contemporaneous risk factors for suicide attempts among adolescents and young adults: developmental changes. J Consult Clin Psychol. 2009;77(2):281–90.

23. Nock MK, Kessler RC. Prevalence of and risk factors for suicide attempts versus suicide gestures: analysis of the National Comorbidity Survey. J Abnorm Psychol. 2006;115(3):616–23.

24. Cougle JR, Keough ME, Riccardi CJ, Sachs-Ericsson N. Anxiety disorders and suicidality in the National Comorbidity Survey-Replication. J Psychiatr Res. 2009;43(9):825–9.

25. Torres AR, Prince MJ, Bebbington PE, Bhugra D, Brugha TS, Farrell M, et al. Obsessive-compulsive disorder: prevalence, comorbidity, impact, and help-seeking in the British National Psychiatric Morbidity Survey of 2000. Am J Psychiatry. 2006;163(11):1978–85.

26. Miché M, Hofer PD, Voss C, Meyer AH, Gloster AT, Beesdo-Baum K, Lieb R. Mental disorders and the risk for the subsequent first suicide attempt: results of a community study on adolescents and young adults. Eur Child Adolesc Psychiatry. 2018;27(7):839–48.

27. Kanwar A, Malik S, Prokop LJ, Sim LA, Feldstein D, Wang Z, Murad MH. The association between anxiety disorders and suicidal behaviors: a systematic review and meta-analysis. Depress Anxiety. 2013;30(10):917–29.

28. Hawgood J, De Leo D. Anxiety disorders and suicidal behaviour: an update. Curr Opin Psychiatry. 2008;21(1):51–64.

29. Bentley KH, Franklin JC, Ribeiro JD, Kleiman EM, Fox KR, Nock MK. Anxiety and its disorders as risk factors for suicidal thoughts and behaviors: a meta-analytic review. Clin Psychol Rev. 2016;43:30–46.

30. Pfeiffer PN, Ganoczy D, Ilgen M, Zivin K, Valenstein M. Comorbid anxiety as a suicide risk factor among depressed veterans. Depress Anxiety. 2009;26(8):752–7.

31. Seo H-J, Jung Y-E, Kim T-S, Kim J-B, Lee M-S, Kim J-M, et al. Distinctive clinical characteristics and suicidal tendencies of patients with anxious depression. J Nerv Ment Dis. 2011;199(1):42–8.

32. Diaconu G, Turecki G. PD and suicidality: is comorbidity with depression the key? J Affect Disord. 2007;104(1–3):203–9.

33. Kim H, Choi KW, Na EJ, Hong JP, Fava M, Mischoulon D, et al. Anxiety attacks with or without life-threatening situations, major depressive disorder, and suicide attempt: a nationwide community sample of Korean adults. Psychiatry Res. 2018;270:257–63.

34. Kilbane EJ, Gokbayrak NS, Galynker I, Cohen L, Tross S. A review of panic and suicide in bipolar disorder: does comorbidity increase risk? J Affect Disord. 2009;115(1–2):1–10.

35. Bolton J, Cox B, Clara I, Sareen J. Use of alcohol and drugs to self-medicate anxiety disorders in a nationally representative sample. J Nerv Ment Dis. 2006;194(11):818–25.

36. Friedman S, Jones JC, Chernen L, Barlow DH. Suicidal ideation and suicide attempts among patients with PD: a survey of two outpatient clinics. Am J Psychiatry. 1992;149(5):680–5.

37. Nock MK, Hwang I, Sampson N, Kessler RC, Angermeyer M, Beautrais A, et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO world mental health surveys. PLoS Med. 2009;6(8):e1000123.

38. Fawcett J. Suicide risk factors in depressive disorders and in PD. J Clin Psychiatry. 1992;53(3, Suppl):9–13.

39. Fawcett J. Comorbid anxiety and suicide in mood disorders. Psychiatr Ann. 2007;37(10):667–71.

40. Fava M, Alpert JE, Carmin CN, Wisniewski SR, Trivedi MH, Biggs MM, et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR∗D. Psychol Med. 2004;34(7):1299–308.

41. Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15(8):868–76.

42. Lento RM, Carson-Wong A, Green JD, AhnAllen CG, Kleespies PM. Is suicidal behavior in mood disorders altered by comorbid PTSD? Crisis. 2019;40:62–6.

43. Klonsky ED, May AM. Differentiating suicide attempters from suicide ideators: a critical frontier for suicidology research. Suicide Life Threat Behav. 2014;44(1):1–5.

44. Joiner T. Why people die by suicide. Cambridge, MA: Harvard University Press; 2005. Retrieved from http://www.hup.harvard.edu/catalog.php?isbn=9780674025493

45. Klonsky ED, May AM. The three-step theory (3ST): a new theory of suicide rooted in the "ideation-to-action" framework. Int J Cogn Ther. 2015;8(2):114–29.

46. O'Connor RC. The integrated motivational-volitional model of suicidal behavior. Crisis. 2011;32:295. https://doi.org/10.1027/0227-5910/a000120.

47. Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite S, Selby EA, Joiner TE Jr. The interpersonal theory of suicide. Psychol Rev. 2010;117(2):575–600.

48. Shneidman ES. A psychological approach to suicide. In: Cataclysms, crises, and catastrophes: psychology in action. Washington, DC: American Psychological Association; 1987. p. 147–83.

49. Wenzel A, Beck AT. A cognitive model of suicidal behavior: theory and treatment. Appl Prev Psychol. 2008;12(4):189–201.
50. Taylor S. Anxiety sensitivity: theory, research, and treatment of the fear of anxiety. London: Routledge; 2014.
51. Stanley IH, Boffa JW, Rogers ML, Hom MA, Albanese BJ, Chu C, et al. Anxiety sensitivity and suicidal ideation/suicide risk: a meta-analysis. J Consult Clin Psychol. 2018;86(11):946–60.
52. Allan NP, Capron DW, Raines AM, Schmidt NB. Unique relations among anxiety sensitivity factors and anxiety, depression, and suicidal ideation. J Anxiety Disord. 2014;28(2):266–75.
53. Stanley IH, Hom MA, Spencer-Thomas S, Joiner TE. Examining anxiety sensitivity as a mediator of the association between PTSD symptoms and suicide risk among women firefighters. J Anxiety Disord. 2017;50:94–102.
54. Capron DW, Fitch K, Medley A, Blagg C, Mallott M, Joiner T. Role of anxiety sensitivity subfactors in suicidal ideation and suicide attempt history. Depress Anxiety. 2012;29(3):195–201.
55. Capron DW, Norr AM, Macatee RJ, Schmidt NB. Distress tolerance and anxiety sensitivity cognitive concerns: testing the incremental contributions of affect dysregulation constructs on suicidal ideation and suicide attempt. Behav Ther. 2013;44(3):349–58.
56. Allan NP, Norr AM, Boffa JW, Durmaz D, Raines AM, Schmidt NB. Examining the unique relations between anxiety sensitivity factors and suicidal ideation and past suicide attempts. Psychiatry Res. 2015;228(3):441–7.
57. Stanley IH, Smith LJ, Boffa JW, Tran JK, Schmidt NB, Joiner TE, Vujanovic AA. Anxiety sensitivity and suicide risk among firefighters: a test of the depression-distress amplification model. Compr Psychiatry. 2018;84:39–46.
58. Berman AL. Risk management with suicidal patients. J Clin Psychol. 2006;62(2):171–84.
59. The Joint Commission. Sentinel Event Alert 56: detecting and treating suicide ideation in all settings. 2016. Retrieved January 21, 2019, from http://www.jointcommission.org/sea_issue_56/
60. Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors. American Psychiatric Association, APA practice guidelines for the treatment of psychiatric disorders: comprehensive guidelines and guideline watches, vol. 1. 1st ed. Arlington: American Psychiatric Association; 2006.
61. National Action Alliance for Suicide Prevention: Transforming Health Systems Initiative Work Group. Recommended standard care for people with suicide risk: making health care suicide safe | Suicide Prevention Resource Center. 2018. Retrieved January 21, 2019, from https://www.sprc.org/resources-programs/recommended-standard-care-people-suicide-risk-making-health-care-suicide-safe
62. Pisani AR, Murrie DC, Silverman MM. Reformulating suicide risk formulation: from prediction to prevention. Acad Psychiatry. 2016;40(4):623–9.
63. Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, et al. Suicide prevention strategies: a systematic review. JAMA. 2005;294(16):2064–74.
64. Kaplan ML, Asnis GM, Sanderson WC, Keswani L, De Lecuona JM, Joseph S. Suicide assessment: clinical interview vs. self-report. J Clin Psychol. 1994;50(2):294–8.
65. Suicide Prevention Resource Center. Zero suicide – in health and behavioral healthcare. 2019. Retrieved January 21, 2019, from http://zerosuicide.sprc.org/
66. Suicide Prevention | VA Community Provider Toolkit. n.d. Retrieved January 21, 2019, from https://www.mentalhealth.va.gov/communityproviders/clinic_suicideprevention.asp
67. Jobes DA. The collaborative assessment and Management of Suicidality (CAMS): an evolving evidence-based clinical approach to suicidal risk. Suicide Life Threat Behav. 2012;42(6):640–53. https://doi.org/10.1111/j.1943-278X.2012.00119.x.
68. Jobes DA. Managing suicidal risk: second edition: a collaborative approach. 2016. Retrieved from https://www.guilford.com/books/Managing-Suicidal-Risk/David-Jobes/9781462526901/reviews
69. VA Suicide Risk Management Consultation Program – MIRECC/CoE. n.d. [general information]. Retrieved January 21, 2019, from https://www.mirecc.va.gov/visn19/consult/

70. Cerel J, Currier GW, Conwell Y. Consumer and family experiences in the emergency department following a suicide attempt. J Psychiatr Pract. 2006;12(6):341–7.
71. Richards JE, Whiteside U, Ludman EJ, Pabiniak C, Kirlin B, Hidalgo R, Simon G. Understanding why patients May not report suicidal ideation at a health care visit prior to a suicide attempt: a qualitative study. Psychiatr Serv (Washington, DC). 2019;70(1):40–5. https://doi.org/10.1176/appi.ps.201800342.
72. Anestis MD, Green BA. The impact of varying levels of confidentiality on disclosure of suicidal thoughts in a sample of United States National Guard Personnel. J Clin Psychol. 2015;71(10):1023–30.
73. Bolton JM, Gunnell D, Turecki G. Suicide risk assessment and intervention in people with mental illness. BMJ (Clinical Research Ed). 2015;351:h4978.
74. Michel K, Jobes DA. Building a therapeutic Alliance with the suicidal patient. Washington, DC: American Psychological Association; 2011. Retrieved from https://www.apa.org/pubs/books/4317248.aspx
75. Lento RM, Ellis TE, Hinnant BJ, Jobes DA. Using the suicide index score to predict treatment outcomes among psychiatric inpatients. Suicide Life Threat Behav. 2013;43(5):547–61.
76. O'Connor SS, Jobes DA, Yeargin MK, Fitzgerald ME, Rodríguez VM, Conrad AK, Lineberry TW. A cross-sectional investigation of the suicidal spectrum: typologies of suicidality based on ambivalence about living and dying. Compr Psychiatry. 2012;53(5):461–7.
77. Kovacs M, Beck AT. The wish to die and the wish to live in attempted suicides. J Clin Psychol. 1977;33(2):361–5.
78. Harvard. Means matter. 2016. Retrieved January 21, 2019, from https://www.hsph.harvard.edu/means-matter/
79. Mérelle S, Foppen E, Gilissen R, Mokkenstorm J, Cluitmans R, Van Ballegooijen W. Characteristics associated with non-disclosure of suicidal ideation in adults. Int J Environ Res Public Health. 2018;15(5):pii: E943.
80. Beck AT, Brown G, Berchick RJ, Stewart BL, Steer RA. Relationship between hopelessness and ultimate suicide: a replication with psychiatric outpatients. Am J Psychiatry. 1990;147(2):190–5.
81. Dazzi T, Gribble R, Wessely S, Fear NT. Does asking about suicide and related behaviours induce suicidal ideation? What is the evidence? Psychol Med. 2014;44(16):3361–3.
82. Hawton K. Restricting access to methods of suicide. Crisis. 2007;28(S1):4–9.
83. Kaplan MS, McFarland BH, Huguet N, Conner K, Caetano R, Giesbrecht N, Nolte KB. Acute alcohol intoxication and suicide: a gender-stratified analysis of the National Violent Death Reporting System. Inj Prev. 2013;19(1):38–43.
84. Wongpakaran N, Wongpakaran T, Lerttrakarnnon P, Jiraniramai S, Sirirak T, Assanangkornchai S, et al. Prevalence, clinical and psychosocial variables of depression, anxiety and suicidality in geriatric tertiary care settings. Asian J Psychiatr. 2019;41:38–44.
85. Jeste ND, Hays JC, Steffens DC. Clinical correlates of anxious depression among elderly patients with depression. J Affect Disord. 2006;90(1):37–41.
86. Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X, et al. Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. Psychol Bull. 2017;143(2):187–232.
87. McLean J, Maxwell M. Risk and protective factors for suicide and suicidal behaviour: a literature review. Edinburgh, Scotland: Scottish Government Social Research; 2008. p. 145.
88. Klonsky ED, Saffer BY, Bryan CJ. Ideation-to-action theories of suicide: a conceptual and empirical update. Curr Opin Psychol. 2018;22:38–43.
89. Tucker RP, Crowley KJ, Davidson CL, Gutierrez PM. Risk factors, warning signs, and drivers of suicide: what are they, how do they differ, and why does it matter? Suicide Life Threat Behav. 2015;45(6):679–89.
90. Conrad AK, Jacoby AM, Jobes DA, Lineberry TW, Shea CE, Arnold Ewing TD, et al. A psychometric investigation of the suicide status form II with a psychiatric inpatient sample. Suicide Life Threat Behav. 2009;39(3):307–20.

91. Linehan MM, Goodstein JL, Nielsen SL, Chiles JA. Reasons for staying alive when you are thinking of killing yourself: the reasons for living inventory. J Consult Clin Psychol. 1983;51(2):276–86.

92. Jobes DA, Mann RE. Reasons for living versus reasons for dying: examining the internal debate of suicide. Suicide Life Threat Behav. 1999;29(2):97–104.

93. Rudd MD, Mandrusiak M, Joiner TE. The case against no-suicide contracts: the commitment to treatment statement as a practice alternative. J Clin Psychol. 2006;62(2):243–51.

94. Bryan CJ, Mintz J, Clemans TA, Leeson B, Burch TS, Williams SR, et al. Effect of crisis response planning vs. contracts for safety on suicide risk in U.S. Army soldiers: a randomized clinical trial. J Affect Disord. 2017;212:64–72.

95. Stanley B, Brown GK. Safety planning intervention: a brief intervention to mitigate suicide risk – ScienceDirect. 2012. Retrieved January 22, 2019, from https://www.sciencedirect.com/science/article/pii/S1077722911000630

96. Stanley B, Chaudhury SR, Chesin M, Pontoski K, Bush AM, Knox KL, Brown GK. An emergency department intervention and follow-up to reduce suicide risk in the VA: acceptability and effectiveness. Psychiatr Serv (Washington, DC). 2016;67(6):680–3.

97. Stanley B, Brown GK. The safety plan treatment manual to reduce suicide risk: veteran version. Washington, DC: United States Department of Veterans Affairs; 2008. Retrieved from http://suicidesafetyplan.com/uploads/VA_Safety_planning_manual.pdf

98. Comtois KA, Linehan MM. Psychosocial treatments of suicidal behaviors: a practice-friendly review. J Clin Psychol. 2006;62(2):161–70.

99. Brown GK, Jager-Hyman S. Evidence-based psychotherapies for suicide prevention: future directions. Am J Prev Med. 2014;47(3 Suppl 2):S186–94.

100. Ahmedani BK, Vannoy S. National pathways for suicide prevention and health services research. Am J Prev Med. 2014;47(3 Suppl 2):S222–8.

101. Batterham PJ, Christensen H, Calear AL. Anxiety symptoms as precursors of major depression and suicidal ideation. Depress Anxiety. 2013;30(10):908–16.

102. Brown LA, Gallagher T, Petersen J, Benhamou K, Foa EB, Asnaani A. Does CBT for anxiety-related disorders alter suicidal ideation? Findings from a naturalistic sample. J Anxiety Disord. 2018;59:10–6.

103. Barlow DH, Farchione TJ, Fairholme CP, Ellard KK, Boisseau CL, Allen LB, Ehrenreich-May J. Unified protocol for transdiagnostic treatment of emotional disorders: therapist guide. 1st ed. Oxford: Oxford University Press; 2011.

104. Bentley KH, Sauer-Zavala S, Stevens KT, Washburn JJ. Implementing an evidence-based psychological intervention for suicidal thoughts and behaviors on an inpatient unit: process, challenges, and initial findings. Gen Hosp Psychiatry. 2018; in press.

105. Norr AM, Allan NP, Reger GM, Schmidt NB. Exploring the pathway from anxiety sensitivity intervention to suicide risk reduction: chained mediation through anxiety and depressive symptoms. J Affect Disord. 2018;231:27–31.

106. Bolton J, Gunnell D, Turecki G. Suicide risk assessment and intervention in people with mental illness. 2015. PubMed – NCBI. Retrieved January 21, 2019, from https://www.ncbi.nlm.nih.gov/pubmed/26552947

107. Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res. 2014;58:161–6.

108. DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry. 2010;71(12):1605–11.

109. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science (New York, NY). 2012;338(6103):68–72.

110. Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy

by experts for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry. 2006;63(7):757–66.

111. Brown GK, Have TT, Henriques GR, Xie SX, Hollander JE, Beck AT. Cognitive therapy for the prevention of suicide attempts: a randomized controlled trial. JAMA. 2005;294(5):563–70.

112. Stanley B, Brown G, Brent D, Wells K, Poling K, Curry J, et al. Cognitive behavior therapy for suicide prevention (CBT-SP): treatment model, feasibility and acceptability. J Am Acad Child Adolesc Psychiatry. 2009;48(10):1005–13.

113. Comtois KA, Jobes DA, O'Connor SS, Atkins DC, Janis K, Chessen CE, et al. Collaborative assessment and management of suicidality (CAMS): feasibility trial for next-day appointment services. Depress Anxiety. 2011;28(11):963–72.

114. Rudd MD, Bryan CJ, Wertenberger EG, Peterson AL, Young-McCaughan S, Mintz J, et al. Brief cognitive-behavioral therapy effects on post-treatment suicide attempts in a military sample: results of a randomized clinical trial with 2-year follow-up. Am J Psychiatr. 2015;172:441–9.

115. McCauley E, Berk MS, Asarnow JR. Efficacy of dialectical behavior therapy for adolescents at high risk for suicide: a randomized clinical trial. JAMA Psychiat. 2018;75(8):777–85.

116. Alavi A, Sharifi B, Ghanizadeh A, Dehbozorgi G. Effectiveness of cognitive-behavioral therapy in decreasing suicidal ideation and hopelessness of the adolescents with previous suicidal attempts. Iran J Pediatr. 2013;23(4):467–74.

117. Nielsen AC, Alberdi F, Rosenbaum B. Collaborative assessment and management of suicidality method shows effect. Dan Med Bull. 2011;58(8):A4300.

118. Linehan MM, Korslund KE, Harned MS, Gallop RJ, Lungu A, Neacsiu AD, et al. Dialectical behavior therapy for high suicide risk in individuals with borderline personality disorder: a randomized clinical trial and component analysis. JAMA Psychiat. 2015;72:475–82.

119. Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, et al. Two year randomized controlled trial and follow-up of DBT vs therapy by experts for suicidal behaviors and BPD. JAMA Psychiat. 2006;63:757–66.

120. Linehan MM, Heard HL, Armstrong HE. Naturalistic follow-up of a behavioral treatment for chronically suicidal parasuicidal borderline patients. Arch Gen Psychiatry. 1993;50:971–4.

121. Mehlum L, Ramberg M, Tormoen AJ, Haga E, Diep LM. Dialectical behavior therapy compared with enhanced usual care for adolescents with repeated suicidal and self-harming behavior: outcomes over a one-year follow-up. J Am Acad Child Adolesc Psychiatry. 2016;55:295–300.

122. Jobes DA, Au JS, Siegelman A. Psychological approaches to suicide treatment and prevention. Curr Treat Options Psychiatry. 2015;2(4):363–70.

Chapter 12
Cognitive Behavioral Therapy for Anxiety Disorders

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Introduction

Anxiety disorders are some of the most common psychological disorders, with a lifetime prevalence of 28.8% and a median age of onset of 11 years [72]. Although anxiety disorders have such a high prevalence, they are also some of the most treatable disorders as many studies have supported the efficacy of cognitive behavioral therapy (CBT) for each anxiety disorder including panic disorder, social anxiety disorder, generalized anxiety disorder, and specific phobia [39, 63]. CBT treatment approaches for each anxiety disorder have a number of common treatment elements such as cognitive restructuring to target maladaptive cognitions and exposure exercises to target behavioral avoidance [39]. Therefore, the basic principles and practice of CBT for anxiety disorders will be covered in this chapter, as well as how CBT has been refined to target the distorted cognitions and avoidance behaviors specific to each anxiety disorder. This chapter will also address the history and development of CBT for anxiety disorders, CBT's efficacy and accessibility, and modifications and future directions for CBT for anxiety disorders.

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History and Development of CBT

Behavioral Therapy

Behavioral theories of anxiety disorders suggest that fear is acquired through classical conditioning and maintained through operant conditioning, specifically the negative reinforcement of avoidance behaviors [90]. For example, a person may develop a specific phobia of dogs after having an adverse experience with a dog. To relieve distress, the person begins to avoid all dogs, but this avoidance maintains the phobia. Therefore, behavioral therapies for anxiety disorders use learning principles to change anxious responding and avoidant behaviors [34, 122]. Behavioral therapy uses a number of different techniques including exposure, relaxation, social skills training, and behavioral activation. For anxiety disorders, exposure to the feared stimuli or situation is the most widely used approach for behavioral therapy [34]. Exposure techniques can be in vivo, imaginal, or interoceptive depending on which anxiety disorder is being treated and what objects, situations, or sensations are feared. Exposure to situations may be in person (in vivo) such as petting a friendly dog or through imagination of situations (imaginal), such as imagining petting a dog. Exposure to feared sensations (interoceptive) includes exercises such as breathing through a cocktail straw to restrict breathing and create the sensation of breathlessness often experienced during panic attacks. By exposing patients to the feared stimuli, exposure techniques aim to extinguish the learned fear.

Initially, it was hypothesized that exposure supported fear extinction through habituation as repeated exposure to a stimulus led to a decrease in fear response to the stimulus [139]. For example, for someone with a dog phobia, repeated exposure to dogs would lead to a decrease in his or her physiological and emotional response (habituation), which would subsequently decrease the initial fear associated with dogs. However, Foa and Kozak [45] later proposed that exposure supports extinction learning by allowing the patient to learn new, corrective information that disconfirms the initial fear associated with stimuli or situation. Therefore, for someone with a dog phobia, repeated exposure to dogs who do not attack would allow that person to learn that most dogs are harmless. Most recently, Craske et al. [28] proposed inhibitory learning theory as an explanation for how exposure works. Inhibitory learning theory suggests that original fear associations must compete with new safety associations acquired during exposures. With repeated exposures, the new, inhibitory associations become stronger than the initial fear associations. Therefore, this disconfirming safety information that most dogs are harmless becomes stronger with repeated exposure, making it more salient than the initial fear association between dogs and danger. Originally thought to be passive, extinction learning during exposures is now believed to be an active learning process in which patients learn new associations of safety with the initially feared stimulus [34, 122]. The decrease in anxiety and fear associated with this new learning also supports a decrease in avoidance behaviors. As avoidance behaviors diminish, patients will approach the initially feared stimuli and situations with more frequency, allowing for further extinction learning to occur.

There are a number of strategies that can be used within exposure therapy to optimize its efficacy for anxiety disorder treatment. These strategies include creating exposures that maximize expectancy violation by maximizing the difference between the expected feared outcome and the true outcome, using deepened extinction in which fears are initially present separately and then later presented together, removing any safety signals, and conducting exposures in a variety of contexts [31]. Safety signals or safety behaviors are defined as overt or covert actions that may be performed to decrease distress and provide reassurance such as always carrying one's medication or cellphone. It is important to remove safety signals or prevent safety behaviors during exposures because the patient may attribute the success of the exposure to the presence of a safety item (e.g., "I didn't have any panic attacks because I had my medication there in case I needed it"), thus interfering with optimal extinction learning [31, 118, 122]. Conducting exposure in a variety of contexts can help counteract context renewal or the return of fear when a stimulus is encountered in a different context than that of the exposure [31, 132]. Multiple contexts can involve doing exposures in different places, at varying times of day and varying days of the week [31].

Cognitive Therapy

Cognitive theories suggest that anxiety disorders result from distorted beliefs about physical or psychological threat [9]. Therefore, in cognitive therapies (CT) for anxiety disorders, patients learn to identify, challenge, and reevaluate these distorted beliefs, which supports alternative rational and adaptive thinking patterns. Cognitive restructuring is a commonly used technique in cognitive therapy for anxiety [122]. First, the clinician teaches the patient how to identify these distorted thoughts and maladaptive beliefs [26]. Often patients will be asked to monitor these thoughts in a daily log [122]. Next, patients learn to evaluate the validity and utility of these distorted cognitions, learning skills to help them reevaluate these thoughts and replace them with more rational alternatives. These skills include considering objective evidence, hypothesis-testing, thought challenging, and recognizing thinking traps such as catastrophizing and overgeneralization [39, 101]. Additionally, clinicians work with the patient to challenge the assumptions surrounding the patient's ability to cope with the worst-case scenarios, by asking questions (e.g., for fear of being embarrassed in front of coworkers, the clinician might inquire if the patient had been embarrassed before, and when they say yes, the clinician would inquire about how they coped with that in the past; [39]).

In cognitive therapy, behavioral experiments, a form of exposure exercises, are used to challenge maladaptive cognitions and assumptions, providing corrective information that helps the patient construct more rational, adaptive thinking patterns [122]. Therefore, unlike exposure exercises in behavioral therapy that aim to habituate the patient to the stimulus, exposure in the form of behavioral experiments in cognitive therapy is carried out to test and challenge the patient's distorted

cognitions and appraisals [34]. Cognitive theories of anxiety disorders posit that behavioral avoidance is a result of maladaptive, distorted beliefs about threat [9]. Therefore, behavioral experiments aim to change these distorted thinking patterns, which will in turn facilitate a decrease in avoidance behavior. For each anxiety disorder, cognitive therapies focus on targeting the specific distorted beliefs in that disorder. For example, in panic disorder, cognitive therapy might focus on the misinterpretations and distorted beliefs surrounding somatic symptoms (e.g., "My heart beating faster means I'm having a heart attack"). Here, a behavioral experiment may include an exercise such as running up and down the stairs to increase the patient's heart rate. Because the patient would not experience a heart attack following this increase in heart rate, this experience would then be used to help challenge the original distorted cognitions surrounding rapid heart rate signifying risk of a heart attack. In contrast to the distorted beliefs surrounding internal sensations in panic disorder, in specific phobia, cognitive therapy would aim to reevaluate the distorted beliefs surrounding the danger of the feared object or situation (i.e., the probability of an airplane crash in flying phobia).

The Efficacy of Behavioral Therapy, Cognitive Therapy, and Their Combination

Both behavioral therapy and cognitive therapy (CT) have been shown to be effective in reducing symptoms of different anxiety disorders. Generally, cognitive behavioral therapy, which combines core treatment constructs of cognitive therapy and behavioral therapy, has shown greater treatment efficacy compared to cognitive therapy alone for most anxiety disorders. However, there are mixed results regarding if cognitive behavioral therapy is superior to behavioral therapy alone for certain anxiety disorders.

Panic Disorder

Behavioral treatments of in vivo exposures for panic disorder have repeatedly shown strong treatment efficacy for the reduction of panic symptoms and agoraphobia, and treatment outcomes are maintained through follow-up assessments [6, 129]. Additionally, cognitive therapy without exposure has shown significant reduction in panic disorder frequency and superior or comparable treatment effects compared to applied relaxation, relaxation training, and imipramine [5, 11, 25, 121]. CT treatment outcomes have also been shown to be maintained at 12-month follow-up [111].

A number of studies comparing the efficacy of cognitive therapy versus behavioral therapy (interoceptive or in vivo exposures) for the treatment of PD suggest that behavioral and cognitive therapies are equally effective in reducing panic fre-

quency and anxiety levels and show similar rates of improvement across treatment [4, 20]. However, it should be noted that due to the relatively low amount of studies examining strictly cognitive therapies for panic disorder, separate effect sizes are often not calculated for cognitive therapies in large treatment efficacy meta-analyses [34]. This makes it difficult to confidently conclude the relative efficacy of these two interventions alone. There have been mixed results from studies comparing cognitive therapy, behavioral therapy, and their combination (CBT approaches). A number of studies have shown that cognitive treatments alone and exposure treatments alone show comparable treatment efficacy as their combination [80, 136]. However, other findings contradicted these conclusions showing superior treatment outcomes for CBT compared to cognitive and behavioral approaches in isolation [86, 112]. In order for future studies to effectively compare the effect sizes of these three treatments, more studies examining the efficacy of strict cognitive therapy for anxiety disorders are needed.

Social Anxiety Disorder

While both cognitive and behavioral therapies have shown efficacy for the treatment of social anxiety disorder (SAD), cognitive behavioral therapy and behavioral therapy alone show superior treatment efficacy as compared to cognitive therapy (CT) alone [42, 50, 126]. One meta-analysis examining treatment outcomes of exposure therapy alone or exposure therapy plus cognitive restructuring found that the two approaches were equally effective at posttreatment and follow-up ranging from 1 to 12 months [42]. Both cognitive behavioral therapy and behavioral therapy alone appear to be equally efficacious and superior to cognitive therapy alone for treatment of SAD.

Specific Phobia

A number of different types of exposure have shown treatment efficacy for specific phobias including systematic desensitization, in vivo exposure, interoceptive exposure, and virtual reality exposure [24]. There is evidence that in vivo exposure is superior to systematic desensitization and indirect exposure (video exposure), but imaginal exposure, interoceptive exposures, and virtual reality exposures show similar treatment outcomes in certain phobias [17, 96, 106, 110]. While cognitive therapy alone shows efficacy for the treatment of some phobias, specifically claustrophobia, it has also been shown to be ineffective for the treatment of other specific phobias including fear of heights, elevators, and darkness [14, 17, 95]. Additionally, cognitive therapy enhances treatment efficacy for in vivo exposure for claustrophobia but not for flying or spider phobia [29, 75, 131]. However, given how effective in vivo exposure is for phobias, a ceiling effect may prevent augmentation

[24]. Overall, behavioral exposures show strong treatment efficacy for specific phobias, and cognitive therapies may enhance this efficacy in some types of phobias but not others.

Generalized Anxiety Disorder

Unlike panic disorder, social anxiety disorder, and specific phobia, exposure targets are less clear in generalized anxiety disorder (GAD, [34]). Therefore, behavioral therapy techniques for generalized anxiety disorder often include imaginal exposures and relaxation training. In multiple meta-analyses, treatments that combine both cognitive and behavioral techniques show significantly higher effect sizes compared to behavioral and cognitive treatments alone [19, 51]. However, the relative efficacy of behavioral and cognitive therapies alone is less clear as Borkovec and Whisman [19] found behavioral strategies to be superior, while Gould and colleagues [51] found no difference between the two approaches. Nevertheless, the superior effects of the combined treatments support the efficacy of CBT for the treatment of GAD.

Basic Principles and Practice

Overview

Although cognitive behavioral therapy has been refined to target the distorted cognitions and avoidance behaviors specific to each anxiety disorder, there are a number of treatment elements that are consistent across all CBT approaches for anxiety disorders [39]. CBT is highly collaborative, goal oriented, active, structured, and short term [69, 122, 141]. The collaborative and goal-oriented nature of CBT is evident in the therapeutic relationship between the clinician and the patient, who work together to identify and challenge maladaptive cognitions and avoidance behaviors, develop alternative coping strategies, and create clear, attainable treatment goals. Homework is also a central feature of CBT, allowing the patient to develop and practice these new techniques and encouraging the patient to be an active participant in treatment. CBT is also short term and structured, such that treatment lasts 8–20 sessions and specific concepts are introduced at each session. CBT is most often delivered as an individual weekly therapy, but there are clinical format modifications that are discussed in this chapter [122].

CBT treatments for different anxiety disorders tend to follow a similar treatment outline and contain overlapping treatment constructs and features including the *three-component model* of emotion (Fig. 12.1), cognitive restructuring, and exposures [39]. Prior to starting CBT, the clinician must determine the patient's diagnosis. This is usually done using a semi-structured interview such as the

Fig. 12.1 *Three-component model* of emotion
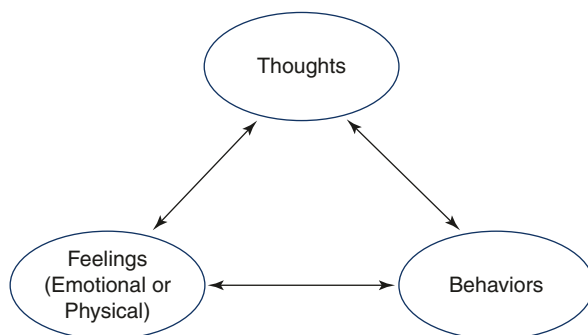
Structural Clinical Interview for DSM-5, Clinician Version (SCID-5-CV; [43]), or the Anxiety and Related Disorders Interview Schedule for DSM 5, Lifetime Version (ADIS-5 L; [21]). In order to track symptom change, the clinician may also opt to use self-report questionnaires throughout treatment. The questionnaires used depend on which anxiety disorder is being treated. Once the diagnosis is determined, CBT begins with a functional assessment of the patient's specific symptoms [39]. Here, the clinician and patient work collaboratively to identify maladaptive thoughts and avoidance behaviors that will become specific targets for treatment. Because CBT is active and requires patients to engage in homework assignments between treatment sessions, it is important to determine a patient's level of motivation upon entering treatment. Oftentime the assignments, such as exposures, can be distressing, so treatment success relies on patients' willingness to participate in these uncomfortable aspects of treatment. In order to support motivation throughout treatment, the clinician can help the patient during this initial phase of treatment to set specific goals for treatment outcomes.

The next step of CBT treatment is psychoeducation. In general, psychoeducation for anxiety disorders highlights the functional role of anxiety, explaining why CBT treatment does not aim to eliminate feelings of anxiety completely [39]. Focusing on the evolutionary benefits of the fight-or-flight response, patients are taught that fear can be adaptive in situations of danger and can help people avoid harm. However, in the case of an anxiety disorder, the distress from having anxiety has become disproportional to a given context or has led to impairment in a given domain, such as work or social life. Furthermore, the *three-component model* is used to explain how thoughts, feelings (emotional or physical sensations), and behaviors are interconnected, and all contribute to anxiety [39]. For example, behavioral avoidance of certain places is maintained through negative reinforcement by decreasing feelings of distress. However, these avoidance behaviors also play a crucial role in maintaining the maladaptive thoughts and cognitions present in anxiety disorders. The *three-component model* can show patients how other treatment constructs such as cognitive restructuring and behavioral exposures (which will be discussed next) each bring about changes in all three components of the model given the components' interconnected nature. During this psychoeducation phase of treatment, clinicians will also emphasize the importance of homework

outside of treatment sessions in order to consolidate different skills that are worked on during the session. Patients are taught the importance of self-monitoring and asked to begin recording triggers for anxiety and the different thoughts, feelings, and behaviors (again, in reference to the *three-component model*) they experience in response to the triggers. What they are asked to monitor may vary slightly between the different anxiety disorders and will be discussed later.

Next, the patient is introduced to the main treatment constructs of cognitive restructuring and exposures. Cognitive restructuring begins with self-monitoring as patients are asked to recognize their automatic thoughts and other maladaptive, dysfunctional beliefs triggered by different situations or emotions. Possible thinking errors, or distorted ways of thinking, for automatic thoughts include jumping to conclusions, emotional reasoning, mind reading, catastrophic thinking, maladaptive thinking, and all-or-nothing thinking [39]. The clinician introduces strategies to help the patient challenge these automatic thoughts and create alternative solutions. This includes recognizing overgeneralizations (i.e., I always sound unintelligent when I speak), catastrophizing (i.e., if I fail this test, I will not pass this class, and I will fail out of school), and reconsidering the actual probability of worst-case scenarios, as well as one's ability to cope with such scenarios [39]. Additionally, patients are asked to identify what behaviors and feelings result from their automatic thoughts, again highlighting the interconnected relationship between thoughts, behaviors, and feelings in the *three-component model*.

Identifying specific avoidance behaviors helps create important targets for exposure exercises. Exposure is a core treatment element of CBT for anxiety disorders. As discussed, exposure supports extinction learning by allowing patients to learn new, corrective information about initially feared stimuli or situations [45]. Clinicians also use exposure exercises to help patients challenge their maladaptive cognitions. For example, if a patient believes they will get fired if they hand in a report that is not completely finished (catastrophizing), a clinician could have them hand in an incomplete report as an exposure to uncertainty. When the patient does not get fired because of this action, the clinician can use this exposure to help the patient challenge the initial catastrophized belief. Examples of exposures used for each anxiety disorder will be discussed in the next sections. Again, emphasizing the collaborative and active nature of CBT, the patient and therapist work together to create a fear and avoidance hierarchy with the patient's most feared situation at the top [39, 74]. By beginning with the least intense exposure exercises, patients can gain a sense of confidence that will support subsequent exposures of more feared stimuli [102]. Initially, exposures are done during treatment sessions with the guidance of the clinician. Additionally, as discussed, the clinician should be vigilant for safety behaviors by inquiring about the function of any behaviors during exposure (e.g., the patient taking a water bottle or asking for reassurance) and work to eliminate these safety behaviors, as they could compromise the extinction learning and success of the exposure exercise [31, 39, 122].

Once treatment concepts are introduced, homework outside of treatment sessions allows for the practicing and consolidation of these concepts. For cognitive restructuring homework, patients are often asked to keep an automatic thought record,

which has them record a situation, the automatic thought associated with the situation, the thinking error associated with that automatic thought, a rating of their mood intensity, a rational response and their belief of the response, and a rerating of their mood intensity [39, 71]. This thought record allows patients to practice cognitive restructuring outside of the treatment sessions and in real time when automatic thoughts arise, helping them learn and consolidate these cognitive restructuring skills. After exposures are practiced during the treatment session, patients are asked to practice exposures at home on their own between sessions in order to help consolidate the skills and prevent avoidance behaviors [18]. Again, it is important for patients not to use safety behaviors or objects during homework exposures in order to facilitate successful learning [31, 39]. The specific thoughts, feelings, and behaviors that are targeted through cognitive restructuring and exposure exercises will differ depending on the type of anxiety disorder and are discussed next.

Panic Disorder

Panic disorder (PD) is characterized by recurrent, unexpected panic attacks and the presence of significant fear and worry surrounding the occurrence of additional attacks or the consequences of panic attacks [1]. A panic attack is characterized by sudden, intense anxiety that peaks quickly and involves symptoms such as increased heart rate, shortness of breath, sweating, and other physiological sensations. Psychoeducation in CBT for PD begins by explaining the adaptive nature of autonomic responding (e.g., the fight or flight response) to actual danger, emphasizes that a panic attack is an intense autonomic response to harmless cues, and demonstrates how PD is maintained through avoidance behaviors and catastrophic misinterpretations of the physiological symptoms associated with fear (APA 2010; [99]). Often, patients with PD view the physiological sensations as intolerable or fear that they will have major consequences (e.g., heart attack). Therefore, cognitive restructuring aims to challenge and change these misinterpretations about somatic symptoms, their consequences, and beliefs about the patient's ability to cope with panic attacks [39].

PD patients can also display a number of avoidance behaviors, including the avoidance of activities that create physical sensations that mirror those in a panic attack (i.e., avoid intense exercise to prevent elevated heart rate). Often, those with PD also experience agoraphobia: Anxiety about being in situations or places in which it is embarrassing or hard to escape if a panic attack occurs. This results in avoidance of these places and situations, such as public transportation or the supermarket. Therefore, the exposure component of CBT for PD involves interoceptive exposures and situational exposures to address the avoidance of somatic symptoms and agoraphobia, respectively [39, 122]. Exposure exercises usually start with interoceptive exposures alone, then situational exposures alone, and then their combination. Interoceptive exposures expose the patient to feared bodily sensations

associated with a panic attack and may involve exercises such as running up flights of stairs (induces pounding heart), spinning in a chair (induces dizziness), and breathing through a straw (induces shortness of breath; APA 2010; [39]). Situational exposures involve exposing the patient to situations or places they have previously avoided because they fear a panic attack will occur and the experience will be embarrassing or hard to escape. Consistent with the general approach of CBT, patients are instructed to practice interoceptive and situational exposures for homework. Finally, interoceptive and situational exposures are combined, allowing the patient to learn that they can handle the feared situations even in the presence of feared somatic symptoms (e.g., straw breathing in a crowded area; APA 2010; [39]). Successful exposure exercises also aid in cognitive restructuring as patients learn that panic attacks do not often happen in the situations they were avoiding or if somatic symptoms or panic attacks do occur, they can handle those experiences. Most often, CBT is administered on a weekly basis. However, there is evidence that for PD a more intensive, short-term version of CBT (i.e., two 9-hour treatment sessions over 2 days) can also be efficacious for treatment [35, 89].

Case Example: Panic Disorder

Laura, a 36-year-old woman sought treatment for panic attacks. During her intake, she described feeling certain she would faint and crash the car if she had a panic attack while driving. She also reported a fear that if she had a panic attack, others would notice, and she would feel embarrassed. To manage her fears, she was avoiding driving and public spaces, especially crowds. During treatment, the therapist provided psychoeducation about the nature of panic as well as information about catastrophic thoughts and probability overestimation. The therapist used Socratic questioning to challenge the catastrophic idea of "If people notice I'm anxious, I will never be able to face them again," and Laura concluded that while unpleasant, she would be able to cope with having others see her panic symptoms. Laura and the therapist also practiced challenging her probability overestimation about fainting while driving. The therapist inquired about how often Laura had fainted during 1 of her 200 past panic attacks (to which Laura responded she never had). This line of questioning helped Laura see that it was unlikely that she would faint while driving.

After completing these cognitive exercises, subsequent sessions focused on interoceptive exposures such as straw breathing, stair running, and head rolling (to induce dizziness). Later sessions involved in vivo exposures, in which Laura practiced riding the train during rush hour and walking quickly up a flight of stairs in a crowded and enclosed public area. The therapist discussed safety behaviors with Laura and identified that keeping her anxiety medication and cell phone with her were ways that she reduced her anxiety. For homework Laura practiced the interoceptive and in vivo exposures while leaving her cell phone or medication at home. In posttreatment assessments, Laura reported that while she still experienced anxiety, she found the experiences less distressing as she now had the tools to cope.

Social Anxiety Disorder

Social anxiety disorder (SAD) is characterized by fear of social or performance situations due to fear of negative evaluation or scrutiny by others [1]. Therefore, cognitive restructuring in CBT for SAD aims to challenge beliefs about perceived negative evaluation by others, one's ability to handle social or performance situations, and the tendency for negative self-focused attention [39]. During cognitive restructuring, patients are asked to gather objective evidence that could support their assumptions of negative evaluation by others and come up with alternative explanations for why people may have behaved the way they did [56]. For example, instead of assuming that a friend did not return a morning greeting because the friend is angry at the patient, the patient could explore other alternatives, such as the friend not having heard the greeting. Through these exercises, patients come to understand that their perception of negative evaluations is actually based on assumptions rather than evidence. Furthermore, the clinician helps the patient challenge beliefs that he or she could not cope with negative outcomes of a social situation. To help alter negative self-focused attention, patients may be asked to focus on environmental aspects during social interactions such as the color of the other person's shirt [39].

Exposures for SAD focus on the social situations that patients have come to avoid due to fear of scrutiny. For someone who is anxious about social interactions, they may be asked to have a conversation with another person and not fill in any silences [39]. Furthermore, social mishap exposures, in which patients are instructed to intentionally create feared social outcomes, such as coming off as unintelligent, are used to demonstrate and disconfirm that such actions will have permanent, intolerable social consequences [62]. For example, a patient may be instructed to ask a stranger for directions to a place that they are standing in front of. As with exposure exercises for any anxiety disorder, it is important for clinicians to discourage the patient from engaging in any safety behaviors, which may include repeatedly rehearsing the exact words of a response or speech to ensure that the patient does not come off as unintelligent [108]. Interoceptive exposures can be combined with situational exposures, helping the patient learn that they can tolerate both the physiological sensations of anxiety and the feared social situation.

Cognitive behavioral group treatment (CBGT), a group approach to CBT, has shown efficacy for the treatment of SAD (e.g., [57–59]). Evidence suggests that social skills training may significantly augment treatment outcomes of [60]. Social skills training for SAD is based on the idea that anxiety in social situations is caused by inadequate social interaction skills [56, 108]. Social skills training involves modeling, behavioral rehearsal, corrective feedback, positive reinforcement, and homework assignments [56, 108]. However, the mechanisms by which social skills training augment CBGT require further investigation. Potentially, social skills training just provides further exposure to feared social situations and additional cognitive restructuring through corrective feedback about the adequacy of the patient's social behavior [56].

Case Example: Social Anxiety Disorder

Charlie, a 20-year-old female, had been experiencing heightened levels of anxiety over the past 2 years in college. She sought treatment due to her growing avoidance of social situations due to fears of being negatively evaluated as unintelligent or socially unskilled. Some general education classes required class presentations or participation in larger lecture halls, and Charlie's grades were dropping as her anxiety led to her avoiding participating or sometimes even attending class at all, if her best friend was not in the class with her. This pressure led to problems in the relationship with her best friend, who felt pressured to change her class schedule to accommodate Charlie. At the same time, her social support from other friends was falling away, as she often took bagged lunches from the dining hall and ate alone in her room, due to the stress she experienced eating in front of others.

Treatment began with Charlie, and the clinician collaboratively derived a model for Charlie's anxiety, focusing on safety behaviors and avoidance. The therapist provided psychoeducation on cognitive restructuring, and Charlie practiced determining whether she had evidence to support her belief that she came across as unintelligent or socially unskilled. Early homework included attending class without her best friend (who was conceptualized as a safety behavior) or sitting toward the front of the room (where she could be seen more easily). Charlie then began conducting exposures practicing giving speeches to confederates and videotaping interactions to test Charlie's beliefs about her social performance. Charlie began to gain evidence that embarrassing herself was less likely than she had previously believed and even if embarrassed, the consequences would not be catastrophic.

At this point, the clinician encouraged Charlie to engage in social mishap exposures. For example, in a bookstore, Charlie asked someone to read the back cover of a book to her because she didn't know how to read (to target her fears of being perceived as unintelligent). The final session included information on relapse prevention. At the end of treatment, Charlie reported greater willingness to speak up in class and was regularly eating in the campus dining hall.

Specific Phobia

Specific phobia is characterized by clinically significant fear of an object or situation, which typically results in avoidance behaviors [1]. Therefore, exposures are used to address avoidance behaviors related to the feared object. For specific phobias, patients confront the actual phobic stimulus during in vivo exposures [24]. Consistent with CBT's general approach to exposures, exposures for specific phobia are conducted in a hierarchal fashion, allowing participants to work their way up to the most feared stimulus or situation. For example, patients with a snake phobia may begin by looking at pictures of snakes but eventually may do an in vivo exposure of holding a live snake. Maladaptive cognitions are also thought to play a role

in maintaining specific phobias [128]. Therefore, cognitive restructuring focuses on challenging the patient's distorted beliefs regarding harmful consequences of the feared object or situation [24]. However, there is mixed evidence regarding if cognitive strategies enhance the effects of exposures for specific phobia [138]. It is possible that in vivo exposures alone counter avoidance behaviors and effectively modify maladaptive beliefs about the feared stimulus [24]. This possibility highlights the importance of the exposure component of CBT for specific phobia as it targets both the "thoughts" and "behavior" components of the *three-component model*.

Case Example: Specific Phobia

Dave, a 40-year-old, married male, presented for treatment for acrophobia or fear of heights. Dave reports that the phobia began ever since he broke his leg falling from a ladder while putting up Christmas lights on his roof a few winters ago. Since the incident, Dave has avoided related tasks such as cleaning the gutters as well as outdoor activities such as hiking in the mountains, something he and his wife and children used to do quite frequently. Dave reports hoping to be able to get back to hiking in time to go on his son's father–son Boy Scout trip in a few months. Dave also reports feeling extremely anxious when he is near windows on any floor above the second floor. He finds himself adjusting his work schedule to make sure he can get to all-staff meetings early to get the seat farthest away from the window. However, Dave's company is moving to the 13th floor of their current building at the end of the year, and he is very worried about how this office change is going to affect his work performance.

Treatment began with Dave and the clinician setting concrete, attainable treatment goals including Dave attending his son's hiking trip and feeling prepared to work in his new office setting. Through psychoeducation, the clinician explained how Dave's avoidance of hiking trips and seats near windows was maintaining his fear of heights. Together, the clinician and Dave created a fear hierarchy to help guide exposure exercises, placing the situations that caused the most fear at the top. Prior to the exposures, the clinician also explained the goal of cognitive restructuring and worked with Dave to pinpoint the distorted beliefs Dave had surrounding his phobia of heights. Exposures started by having Dave stand near the window on the 4th and 5th floors of buildings and look out, eventually working toward windows on higher-level floors. Next, Dave did exposures that involved standing near the railing of balconies, again, working from lower to higher stories of the building. Lastly, Dave did an in vivo exposure of hiking up a mountain and walking around at the top near the edge. Dave was instructed to practice these exposures for homework. The clinician and Dave also worked on restructuring his distorted cognitions, including overestimating the chances of falling over a railing or a cliff's edge. By the end of treatment, Dave reported that he had started to join his family on their weekly hiking trips again and was able to stay focused and engaged in staff meetings while sitting near the window.

Generalized Anxiety Disorder

GAD is characterized by excessive, uncontrollable worry about a number of events or activities (i.e., relationships, health, finances; [1]). In the CBT conceptualization of GAD, patients engage in worry to give themselves the perception of control over uncertain outcomes and a false sense of preparedness for catastrophe because ambiguous and uncertain outcomes are interpreted as potentially dangerous [39]. The cycle of worry becomes negatively reinforced because catastrophic outcomes often do not happen, which links the act of worrying to the catastrophe not occurring. Additionally, worry suppresses emotional and physiological responding, preventing the patient from fully experiencing or processing the topics being worried about [84]. Therefore, worry is also negatively reinforced given its ability to decrease emotional and physiological responding in times of anxiety.

During cognitive restructuring, clinicians work with their patients to challenge the probability of assumed catastrophic outcomes and help them consider other, more likely outcomes. Clinicians also work with their patients to challenge beliefs about their inability to cope with the uncertainty of specific situations that cause worry. The mindfulness skill of present focused attention is sometimes incorporated into CBT for GAD in order to help stop the future-focused worry cycle [109]. Exposure in CBT for GAD may be imaginal or behavioral [39]. During imaginal exposures, patients are asked to imagine the worst-case scenario in vivid detail while incorporating cognitive restructuring techniques to help challenge catastrophic assumptions and beliefs of being unable to tolerate uncertainty. Behavioral exposures focus on preventing behaviors that are driven by anxiety and worry [39]. To reduce uncertainty, patients may proofread emails many times or constantly seek reassurance for others about decisions. Exposures for these behaviors could involve sending emails without proofreading or not seeking reassurance. These behavioral exposures help the patient learn they can tolerate this uncertainty and that feared outcomes do not often happen.

In CBT for GAD, additional skills are taught that help stop the cycle of worry. Self-monitoring often of behavioral exposures involves keeping a worry record, which includes triggers for worries, levels of anxiety produced by the worry, content of the worry, and behaviors fueled by the worry. Patients may also be taught relaxation techniques such as progressive muscle relaxation [142]. Progressive muscle relaxation and other relaxation skills target the physical tension present in GAD and help the patient relax on command to interrupt the worry cycle.

Case Example: Generalized Anxiety Disorder

Doug, a 27-year-old male, reports that he spends much of the day worrying about a number of topics, including his job, his relationship, and his parents' health. He reports feeling extremely anxious about making mistakes at work and feels that if

he does make a mistake, he will be fired. Therefore, he checks over all his work extremely thoroughly often leading him to stay at the office much longer. He also expresses anxiety surrounding his relationship with his girlfriend and fears that she is going to break up with him, which is only exacerbated by his need to cancel their plans when he works late. Doug also reports feeling extremely anxious about his parents' health, fearing that one of them will be diagnosed with an illness or pass away suddenly. His recently learned his Dad had been experiencing some joint pain. Despite the doctor reporting that it is arthritis, Doug constantly worries it is something much more serious and that the doctor has simply missed other signs for a correct diagnosis. Additionally, Doug reports feeling irritable, restless, and keyed up and has difficulty falling asleep. When asked about muscle tension, he expresses feeling major muscle tension in his neck and shoulders but attributes the tension to his new job in which he sits at a desk during the day.

First, Doug and the clinician worked together to identify both his maladaptive beliefs and avoidance behaviors. Using psychoeducation and the three-component model, the clinician showed Doug how these specific thoughts and actions create and maintain his anxiety. Cognitive restructuring was used to reevaluate the probability of his worries actually happening as well as his own ability to cope with the situation if they did happen. For example, Doug was asked to find objective evidence for his worries that his girlfriend wanted to break up; these thoughts were disconfirmed when he could not find much evidence for this belief.

Different exposures techniques were also used during treatment. For example, Doug was asked to do a behavioral exposure where he completed work without checking it over and handed in what was done at the end of the work day even though it was not complete. These exposures helped Doug learn he could handle the uncertainty of not knowing if there were mistakes in his work and disconfirmed his concern that he would be fired for incomplete work. In terms of his father having an illness, both cognitive restructuring and imaginal exposures were used to help Doug reevaluate his ability to cope with the worst-case scenario if it did happen. Lastly, Doug was taught progressive muscle relaxation to help target his tension symptoms. Doug was instructed to use such relaxation techniques between sessions when he felt he cannot control his worry in order to help stop the worry cycle and decrease anxiety.

Efficacy of CBT for Anxiety Disorders

There is a robust research literature examining the efficacy of CBT for anxiety disorders, and the beneficial effects are considered well established [123]. Meta-analyses of randomized controlled trials of CBT for anxiety suggest that CBT is more efficacious than no treatment and more efficacious than pill or psychotherapy placebos [23, 66, 93]. Out of the many disorder-specific CBT protocols that have been studied, anxiety disorder protocols produce some of the strongest results [63]. Though there is a great deal of research, there are some limitations to the available

literature. For example, many of the seminal meta-analyses and reviews were published over a decade ago and include diagnoses that are no longer classified as anxiety disorders by the DSM-5 (e.g., obsessive–compulsive disorder and post-traumatic stress disorder). It is possible that these meta-analyses and reviews may produce different findings when restricted to the current definition of anxiety disorders. Additionally, meta-analyses compared studies with various placebos, such as placebo medication or nondirective therapy, so it is not possible to determine the efficacy of treatment as related to a specific control condition [97].

While broad efficacy of CBT for anxiety disorders has been demonstrated consistently, there are many formats of delivery for these treatments that are now being tested to improve accessibility and meet the high demand for these treatments. As previously mentioned, CBT studies have typically explored individual CBT. Individual CBT for anxiety disorders in an outpatient clinic found that those who were classified either as responders or remitters after three or more sessions of CBT maintained treatment success at 1-year follow-up [36]. Group treatments, which improve accessibility by allowing one therapist to serve multiple clients at once, have also been studied. Group CBT for social anxiety was found to yield greater improvements than a waitlist control [49]. Group CBT for GAD was also found to yield superior outcomes compared to a waitlist control [37]. When CBT for panic disorder was compared in group and individual formats to waitlist control, both CBT groups achieved clinically significant results, with neither CBT group outperforming the other at posttreatment [115]. Regardless of whether the treatment is delivered individually or in a group, CBT has been found to be more effective than a variety of other treatments [10].

For treatment over shorter periods, intensive treatments have been developed and show efficacy for treating anxiety disorders. For example, 9 hours of CBT over 2 days is effective in reducing panic in most (60%) of patients [35]. Treatments as short as 1 day have also been shown efficacious for some specific phobias [96]. Two weeks of intensive group therapy for social anxiety disorder showed significant decreases in symptoms compared to a waitlist control [88]. These treatments may be useful for patients who have an upcoming deadline for treatment (e.g., a flying phobia patient who needs to take a flight for work in the next month), for clients in rural areas who do not have CBT for anxiety providers living nearby who must travel to another location for treatment, or for individuals who simply want results more quickly.

Computerized CBT has also been shown to be effective in treating anxiety disorders [3]. Programs such as *Beating the Blues*™, a computerized CBT protocol for depression and anxiety, have been shown to decrease anxiety symptoms with only minimal clinical supervision and to improve work and social life of users [104]. A computerized CBT program for anxiety, *FearFighter*, has been recommended by a government regulatory body in England and Wales [32]. In a randomized controlled trial, comparing *FearFighter* to individual, face-to-face CBT, as well as to a placebo computerized relaxation condition, *FearFighter* reduced clinician time by 73% (compared to the face-to-face CBT) without compromising efficacy [81].While Internet-based CBT is effective without additional therapist support (contact that is either supportive or facilitative of the CBT materials), some studies suggest computerized

CBT shows even greater efficacy with added therapist support [120]. There is now a large literature supporting the use of computerized CBT, but providers are still lagging in recommending computerized CBT to patients. In one study, under 3% of therapists used computerized CBT. Educating providers on the efficacy of computerized CBT will be necessary to the increasing use of these treatments, as most providers surveyed were not aware of the strong research support [135]. Overall, computerized CBT is an efficacious and accessible treatment format for anxiety. Future work should focus on how to increase clinician knowledge and use of these treatments.

In addition to disorder-specific protocols, there is also evidence supporting the efficacy of transdiagnostic CBT (e.g., [40, 83]). Transdiagnostic CBT describes a protocol that is designed to treat a spectrum of disorders and can be administered to either individuals or groups. Transdiagnostic CBT has been shown to have equal efficacy and a lower dropout rate than other established anxiety treatments, such as relaxation training [91]. Compared to the more established disorder-specific CBTs for anxiety, transdiagnostic CBT for anxiety has shown comparable efficacy [92].

Despite the strong evidence for CBT for anxiety, there are many patients who do not respond to the treatment [127]. CBT for anxiety has a 34–36% nonresponder rate, meaning that over one-third of enrolled patients do not achieve clinically significant reductions in their symptoms over the course of treatment [127]. Several factors have been found that relate to reduced efficacy. Patients' executive function (EF) abilities appear related to outcomes. A study of older adults found that patients with low EF pre- to posttreatment did not respond to CBT for anxiety [87]. Meta-regression of factors predicting outcome suggests that CBT is significantly less effective for individuals with severe pathology, which is a limitation of the treatment [53]. Additionally, many patients drop out of treatment before completing. One study of CBT for generalized anxiety disorder found that one in six clients dropped out of treatment [48]. A meta-analysis of dropout by disorder found that this rate (around 17%) persisted across anxiety disorders, suggesting that many patients are struggling to engage fully with CBT [124]. Dropouts have been found to experience higher dissatisfaction and poorer treatment outcomes [15, 73]. Future research will be needed to improve CBT for individuals with severe pathology and to reduce dropout rates.

Generalizability of CBT for Anxiety

In addition to establishing efficacy of CBT for anxiety, effectiveness of CBT for anxiety (how well CBT generalizes to less controlled, real-world settings) has also been demonstrated. Individual studies of effectiveness of CBT for panic disorder show similar response rates to efficacy studies of CBT for panic [113]. Results from a meta-analysis of effectiveness studies found that the results in effectiveness studies were similar to those of efficacy trials [123]. Computerized CBT has been supported in effectiveness trials. In a primary care setting, patients showed substantial improvements, even with the support of only novice clinicians [30]. Formats of

CBT that have been tested for generalizability have found similar results to controlled trials, suggesting that CBT is useful in real-world settings, such as hospitals, private practices, and clinics.

Cultural adaptations to CBT are explored as a means of improving generalizability of the treatment (see Chap. 4). There is reason to believe that treatment efficacy may depend on one's culture or identity. For example, in a study of panic disorder, African Americans had lower response rates to CBT for panic attacks than white Americans did [85]. Other studies had conflicting results, suggesting that white and African Americans responded at equal rates to CBT for panic [85]. Additional rationale for cultural adaptation includes the support for culture-specific anxiety diagnoses in the DSM, such as *ataque de nervios* in Latinx individuals (in which disordered "nerves" are believed to lead to a loss of control), *khyâl* attacks for Cambodians (in which blood is believed to move upward in the body causing bodily problems and often lead to a fear of death), or *taijin kyofusho* for a Japanese client (a type of social anxiety focused more on making others uncomfortable). Due to the different cognitions that may accompany a culture-specific anxiety presentation, asking about the meaning the patient ascribes to symptoms such as nightmares or startling easily is recommended. These meanings can then be considered when challenging thought errors or when structuring exposures. There may also be benefits to considering the role of metaphor or analogy in sessions. Otto [98] suggests that advantages to using metaphors in treatment include helping increase patient understanding of concepts and improving retention of therapeutic information. Proverbs or stories that are specific to one's native language or culture may be more useful than unfamiliar stories or analogies. The use of culturally appropriate material may improve therapeutic alliance, enhancing CBT for anxiety.

Protocols that are specific to particular cultural groups do exist, though research on cultural adaptations is sparse and the majority of research study populations are white, non-Hispanic individuals. There is evidence to suggest that culturally sensitive CBT is superior to other treatments [54]. Unfortunately, due to the lack of data available and the limitations of the methodology of current studies, cultural adaptations don't always lead to improved outcomes [13]. This may be less a reflection of the utility of cultural adaptation and more a suggestion that constructs of culture are poorly understood. Therefore, homogeneity of cultural tailoring may not be useful. Future research is needed to refine constructs of cultures and adapt protocols based on the improved construct knowledge. Until then, patients may benefit from clinicians' multicultural knowledge and tailoring of CBT to an individual's culture and values [134].

Accessibility

Despite the high numbers of individuals affected by anxiety disorders and the robust evidence for CBT for anxiety, most individuals with anxiety do not receive efficacious treatment [27]. One common problem is practitioners who advertise

their practice as cognitive behavioral, but do not utilize the active ingredients of CBT protocols (see Chap. 18). The American Psychiatric Association recommends exposure-based CBT as the first-line treatment for anxiety disorders, yet therapist surveys suggest that community providers (even if self-identifying as having a cognitive-behavioral orientation) rarely use exposure-based treatments for anxiety [46]. This avoidance of exposure is hypothesized to be due to a host of factors including logistics (exposure sessions often run beyond the typical 50-minute therapy hour), workplace policies (e.g., not being allowed to travel off-site with a client for exposures like driving or going to crowded areas), negative therapist beliefs about exposure therapy (e.g., exposure being unethical or cruel or that exposure may harm the therapeutic relationship), or lack of training on effective use of exposure [61]. Future research on how best to train therapists about exposure may be helpful in the long-term goal of increasing community providers' comfort with and use of exposure.

There is growing evidence supporting more accessible and affordable formats of CBT (e.g., transdiagnostic and Internet-based CBT (iCBT)), which may lead to improved accessibility [92]. iCBT can be either mobile or web based. For a subset of applications, the therapeutic content is not reliant on Internet access, so the interventions can be accessed even when clients are traveling or when Internet is not available. For this reason, and due to the growing access to the Internet, mobile and web-based applications reduce barriers to accessing care [103]. These formats also extend care beyond face-to-face visits, providing helpful reminders about how to practice skills or offering options to track symptoms [22]. Mobile and web-based applications have also been shown to increase patient engagement with care and compliance [47]. Internet-based CBT is effective without additional therapist support though efficacy has shown to increase with added therapist support [120]. iCBT also offers the benefits of being in line with best practice [41] and reducing costs of treatment [38].

In addition to logistical benefits of iCBT, mobile and Internet-based applications also benefit from good credibility ratings. Studies suggest that patients see iCBT as an acceptable option, but further research is needed to determine the number of individuals with anxiety disorders using iCBT [3, 30]. Also promising for the utility of iCBT is evidence suggesting that adherence to iCBT is similar to face-to-face CBT. A trial comparing the two treatment methods found that participants in face-to-face CBT completed an average of 83.9% of the treatment sessions and participants in iCBT completed 80.8% of sessions [130]. Given the logistical advantages and similar adherence and outcomes to face-to-face treatment, these mobile and web-based CBT interventions may become more popular and improve access to quality treatment for anxiety.

For clients who do not have web or mobile access, ability, or interest, transdiagnostic treatments are another avenue to increase accessibility of CBT for anxiety. Lack of training is often cited as a barrier for therapists wanting to provide evidence-based treatment like CBT [12]. There are several developments that are beginning to help lower the barrier. In train-the-trainer models, an expert trains other practitioners to provide an evidence-based treatment [141]. This model has been

shown to have support in pilot studies on CBTs for eating disorders and substance abuse [116, 141], and train the trainer may be useful in the dissemination of CBT for anxiety. Future studies examining train-the-trainer models for CBT for anxiety are necessary to determine if the model works well for anxiety disorders. Transdiagnostic CBT also lowers this barrier to evidence-based care, as therapists with training in this one protocol can treat a range of disorders. Studies have also supported the efficacy of transdiagnostic CBT for anxiety in a group format, which allows even greater accessibility [92]. For clients with comorbid disorders, this type of treatment may also provide a useful option (rather than completing multiple, disorder-specific protocols), as clients with and without comorbidities showed similar improvements in their primary diagnoses (Norton et al., 2012). Having a singular treatment target a variety of anxiety presentations, especially when delivered in a group, saves clients both time and money and may make individuals more willing to seek treatment.

There are also barriers beyond universal factors such as money, location, or time. Intellectual and physical disabilities are infrequently discussed but are relevant considerations for treatment accessibility. Some physical disabilities, such as blindness, may require tailoring of the protocol (e.g., consideration of how to adapt drawing an anxiety model). Clients who are deaf may have larger barriers, such as finding trained therapists who can sign or skilled interpreters. Intellectual disabilities have been a greater focus of research, and studies find that clients with intellectual disabilities can effectively recognize and label emotions [70] and link emotions and events [70, 94]. However, effectiveness appears to be correlated with verbal IQ, and the positive gains are not maintained at 3- and 6-month follow-ups [137]. These individuals are often also excluded from community samples of randomized controlled trials, and individuals with physical disabilities are often not recruited or acknowledged in discussions of CBT accessibility. Future research will be necessary to determine how to best tailor CBT for physical and intellectual disabilities.

Modifications of Traditional CBT and Future Directions

Combining CBT and Medication

The pharmacotherapy of anxiety disorders is detailed in Chap. 13. There have been mixed findings regarding CBT's combination with pharmacological interventions providing superior treatment outcomes for anxiety disorders compared to CBT alone [7, 8, 16, 44, 65]. One meta-analysis of randomized controlled trials that compared combined treatments with pharmacological and CBT treatments alone showed no significant differences across treatment outcomes for social phobia or GAD [44], but a second meta-analysis examining these treatments and their combination found that the combination of CBT and medication showed higher efficacy than either treatment alone [7]. Additionally, a meta-analysis of placebo-

controlled trials comparing combination treatments to CBT plus placebo found only modest, acute benefits to combined treatment with no long-term benefits sustained at 6-month follow-up [65].

Not only have results from meta-analyses been mixed, but studies on specific anxiety disorders have also shown mixed results. Foa and colleagues [44] found that, for panic disorder, combined treatment was superior to CBT alone at posttreatment but was associated with greater relapse [44]. In contrast, Barlow et al. [8] found that for panic disorder CBT plus imipramine did not result in superior treatment outcomes compared to CBT plus placebo at both posttreatment and follow-up periods. For social anxiety disorder, phenelzine sulfate in combination with group CBT showed significantly better treatment outcomes than group CBT or medication alone [16]. However, the combination of CBT and fluoxetine showed similar treatment outcomes to CBT plus placebo for the treatment of social anxiety disorder [33]. Therefore, the efficacy of the combination of CBT and medication may vary among disorders as well as among medication types. Given that combining CBT with anxiolytic pharmacotherapies, such as selective serotonin reupdate inhibitors, has shown mixed results and only modest gains, modern approaches to pharmacological augmentation has shifted to explore which medications may act as cognitive enhancers, augmenting the core learning processes of CBT [67].

Combining CBT and D-Cycloserine

One cognitive enhancer in particular, D-cycloserine (DCS), has emerged as a promising pharmacological agent for the augmentation of CBT. Animal studies suggest that DCS, an N-methyl-D-aspartate (NMDA) partial agonist, can facilitate fear extinction learning when given before or shortly after exposure to the feared stimuli [77, 78, 133]. In humans, the combination of DCS and CBT has shown to be superior to CBT and placebo in a number of different anxiety disorders, but the results are mixed [52, 64, 100, 107, 125]. In a study of subjects with acrophobia, those given DCS prior to virtual reality exposure sessions not only show significantly more extinction learning posttreatment and at 3-month follow-up but also reported less avoidance of heights after study completion compared to those given placebo; this suggests that DCS both enhances extinction learning and supports confrontation of feared stimuli [107]. In contrast, Tart et al. [125] failed to find any significant differences in treatment outcomes between DCS and placebo groups in another sample of individuals with acrophobia. Similarly, mixed results have been found for panic disorder. Otto et al. [100] found that individuals who received DCS prior to interoceptive exposure showed significantly better treatment outcomes at posttreatment and 1-month follow-up. However, Siegmund et al. [117] failed to find statistically significant differences in treatment outcomes between DCS and placebo groups in a sample of patients with panic disorder and agoraphobia. Meanwhile, in two studies of social anxiety disorder,

participants who received DCS compared to placebo prior to exposure showed better treatment outcomes at posttreatment and 1-month follow-up [52, 64].

Evidence suggests that the ability for DCS to enhance exposure therapy may depend on the success of the exposure session; DCS may only be advantageous to CBT when exposure sessions are successful [119]. In a study of social anxiety disorder patients, patients who received DCS prior to exposure and reported low fear following the exposure, suggesting that it was a success, showed significantly greater clinical improvement at the next session compared to the placebo group [119]. Patients who received DCS prior to exposure and reported high fear at the end of an exposure, suggesting it was not a success, actually showed less clinical improvement at the next session compared to the placebo group [119]. Furthermore, at posttreatment, those in the DSC group reported lower clinical severity compared to the placebo group when their average fear following exposures was in the low to moderate range [119]. This suggests that the success of the exposure session may determine the efficacy of DCS for augmenting CBT, which may also explain some of the mixed findings among previous studies. For example, post hoc reanalysis of the study by Tart et al. [125] found that for those with successful exposure sessions, the DCS group showed significantly more improvement compared to placebo [119]. However, those with unsuccessful exposures sessions showed significantly less improvement compared to placebo [119]. Potentially, DCS supports fear memory reconsolidation and therefore shows negative effects on treatment outcomes in CBT when exposures are unsuccessful [68, 119].

CBT and ABM

The use of attention bias modification (ABM) for the treatment of anxiety disorders arises from theoretical models that suggests anxiety is caused and maintained by biases in early processing, specifically attention and interpretation [82, 105]. In terms of attention biases, those with anxiety disorders are thought to allocate excessive attentional resources to threat [105]. Which type of threat will vary depending on the anxiety disorder? For example, those with social anxiety disorder are biased toward attending to social threats. MacLeod et al. [79] were one of the first to demonstrate that training individuals to focus their attention away from threat reduced their emotional response to subsequent stressors, suggesting that this technique, ABM, may show therapeutic effects for those with anxiety disorders. A standard ABM task presents a threat cue and a nonthreat cue simultaneously on a computer screen. Then a probe appears in the position of one of the two cues, and patients are asked to identify the probe (i.e., press the key on the keyboard that is used as the probe). Attention bias is assessed by one's latency to respond to the probe in threat and nonthreat cue positions. ABM involves replacing the nonthreat cue in the majority of trials in order to shift the attention toward the nonthreat stimuli and away from the threat stimuli. Several randomized controlled trials have dem-

onstrated that ABM can reduce anxiety symptoms as a stand-alone treatment (e.g., [2, 55, 114]).

More recent research has examined if attention bias modification can augment CBT treatment outcomes. However, mixed results have been found. In a study of adults with SAD, CBT plus attention bias retraining and CBT plus placebo showed no significant differences in treatment outcomes; both treatment approaches showed significant reductions in diagnostic severity and social anxiety symptoms [105]. However, a second study examining adults with SAD found that group CBT plus ABM showed significantly higher reductions in clinician-rated SAD symptoms compared to CBT plus placebo at posttreatment and 3-month follow-up [76]. Nevertheless, the two groups showed similar reduction in self-reported symptom reduction and attention-bias measures, suggesting that modifying attentional biases did not mediate the group differences in clinician-rated severity [76]. Overall, there are inconclusive results of ABM's ability to augment CBT for anxiety disorders.

Summary

While behavioral therapy and cognitive therapy show efficacy for the treatment of anxiety disorders, several studies have shown that their combination is more efficacious than either treatment approach alone. Such findings supported the development of cognitive behavioral therapy for anxiety disorders. Cognitive behavioral therapy (CBT) utilizes aspects of both cognitive therapy and behavioral therapy, and its efficacy for the treatment of panic disorder, social anxiety disorder, generalized anxiety disorder, and specific phobia is well established [123]. CBT is highly collaborative, goal oriented, active, structured, and short term [69, 122, 141]. While cognitive behavioral therapy has been refined to target the distorted cognitions and avoidance behaviors specific to each anxiety disorder, there are a number of common treatment elements including the *three-component model* of emotion, cognitive restructuring, and exposures that are maintained across CBT for anxiety disorders [39].

CBT done in a group format, through short-term intensive treatment sessions, and using Internet-based protocols have all shown efficacy in the treatment of anxiety disorders; these adjustments to the delivery of CBT helps increase its accessibility [3, 35, 37, 88]. It has also been demonstrated that CBT can generalize to less controlled, real-world settings [123]. However, more research is needed to understand how CBT protocols for anxiety disorders can be adapted to specific cultural groups and whether these culturally sensitive adaptations are superior to existing treatments [54]. More recent research focusing on the augmentation of CBT with medication, DCS, or ABM has produced mixed results [7, 105, 119]. Given that anxiety disorders are of high prevalence and CBT is an efficacious treatment approach for these disorders, research continues to examine ways in which to optimize CBT for the treatment of anxiety disorders.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.
2. Amir N, Beard C, Taylor CT, Klumpp H, Elias J, Burns M, Chen X. Attention training in individuals with generalized social phobia: a randomized controlled trial. J Consult Clin Psychol. 2009;77(5):961.
3. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. PLoS One. 2010;5(10):e13196.
4. Arntz A. Cognitive therapy versus interoceptive exposure as treatment of panic disorder without agoraphobia. Behav Res Ther. 2002;40(3):325–41.
5. Arntz A, Van Den Hout M. Psychological treatments of panic disorder without agoraphobia: cognitive therapy versus applied relaxation. Behav Res Ther. 1996;34(2):113–21.
6. Bakker A, van Balkom AJ, Spinhoven P, Blaauw BM. Follow-up on the treatment of panic disorder with or without agoraphobia: a quantitative review. J Nerv Ment Dis. 1998;186(7):414–9.
7. Bandelow B, Seidler-Brandler U, Becker A, Wedekind D, Rüther E. Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders. World J Biol Psychiatry. 2007;8(3):175–87.
8. Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA. 2000;283(19):2529–36.
9. Beck AT, Emery G, Greenberg R. Anxiety disorders and phobias: a cognitive perspective. New York: Basic Books; 1985.
10. Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive therapy of depression: a treatment manual. New York: Guilford Press; 1979.
11. Beck JG, Stanley MA, Baldwin LE, Deagle EA, Averill PM. Comparison of cognitive therapy and relaxation training for panic disorder. J Consult Clin Psychol. 1994;62(4):818.
12. Becker C, Zayfert C, Anderson E. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. Behav Res Ther. 2004;42(3):277–92.
13. Benuto LT, Casas J, O'Donohue WT. Training culturally competent psychologists: a systematic review of the training outcome literature. Train Educ Prof Psychol. 2018;12(3):125–34.
14. Biran M, Wilson GT. Treatment of phobic disorders using cognitive and exposure methods: a self-efficacy analysis. J Consult Clin Psychol. 1981;49(6):886–99.
15. Björk T, Björk C, Clinton D, Sohlberg S, Norring C. What happened to the ones who dropped out? Outcome in eating disorder patients who complete or prematurely terminate treatment. Eur Eat Disord Rev. 2009;17(2):109–19.
16. Blanco C, Heimberg RG, Schneier FR, Fresco DM, Chen H, Turk CL, et al. A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. Arch Gen Psychiatry. 2010;67(3):286–95.
17. Booth R, Rachman S. The reduction of claustrophobia-I. Behav Res Ther. 1992;30(3):207–21.
18. Borkovec TD, Newman MG, Pincus AL, Lytle R. A component analysis of cognitive-behavioral therapy for generalized anxiety disorder and the role of interpersonal problems. J Consult Clin Psychol. 2002;70(2):288.
19. Borkovec TD, Whisman MA. Psychological treatment for generalized anxiety disorder. In: Mavissakalian MR, & Prien RF, (Eds.). Long-term treatments of anxiety disorders. Washington, DC: American Psychiatric Association; 1996;171–99.
20. Bouchard S, Gauthier J, Laberge B, French D, Pelletier MH, Godbout C. Exposure versus cognitive restructuring in the treatment of panic disorder with agoraphobia. Behav Res Ther. 1996;34(3):213–24.
21. Brown TA, Barlow DH. Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5L): Lifetime Version. Client Interview Schedule. Oxford: Oxford University Press; 2014.

22. Bush NE, Skopp N, Smolenski D, Crumpton R, Fairall J. Behavioral screening measures delivered with a smartphone app: psychometric properties and user preference. J Nerv Ment Dis. 2013;201(11):991–5.
23. Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JA, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: a meta-analysis of randomized placebo-controlled trials. Depress Anxiety. 2018;35(6):502–14.
24. Choy Y, Fyer AJ, Lipsitz JD. Treatment of specific phobia in adults. Clin Psychol Rev. 2007;27(3):266–86.
25. Clark DM, Salkovskis PM, Hackmann A, Middleton H, Anastasiades P, Gelder M. A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. Br J Psychiatry. 1994;164(6):759–69.
26. Clark DA. Perceived limitations of standard cognitive therapy: a consideration of efforts to revise Beck's theory and therapy. J Cogn Psychother. 1995;9(3):153.
27. Collins KA, Westra HA, Dozois DJ, Burns DD. Gaps in accessing treatment for anxiety and depression: challenges for the delivery of care. Clin Psychol Rev. 2004;24(5):583–616.
28. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behav Res Ther. 2008;46(1):5–27.
29. Craske MG, Mohlman J, Yi J, Glover D, Valeri S. Treatment of claustrophobias and snake/spider phobias: fear of arousal and fear of context. Behav Res Ther. 1995;33(2):197–203.
30. Craske MG, Roy-Byrne PP, Stein MB, Sullivan G, Sherbourne C, Bystritsky A. Treatment for anxiety disorders: efficacy to effectiveness to implementation. Behav Res Ther. 2009;47(11):931–7.
31. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: an inhibitory learning approach. Behav Res Ther. 2014;58:10–23.
32. Cuijpers P, Marks IM, van Straten A, Cavanagh K, Gega L, Andersson G. Computer-aided psychotherapy for anxiety disorders: a meta-analytic review. Cogn Behav Ther. 2009;38(2):66–82.
33. Davidson JR, Foa EB, Huppert JD, Keefe FJ, Franklin ME, Compton JS, et al. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. Arch Gen Psychiatry. 2004;61(10):1005–13.
34. Deacon BJ, Abramowitz JS. Cognitive and behavioral treatments for anxiety disorders: a review of meta analytic findings. J Clin Psychol. 2004;60(4):429–41.
35. Deacon B, Abramowitz J. A pilot study of two-day cognitive-behavioral therapy for panic disorder. Behav Res Ther. 2006;44(6):807–17.
36. DiMauro J, Domingues J, Fernandez G, Tolin DF. Long-term effectiveness of CBT for anxiety disorders in an adult outpatient clinic sample: a follow-up study. Behav Res Ther. 2013;51(2):82–6.
37. Dugas MJ, Ladouceur R, Léger E, Freeston MH, Langlois F, Provencher M, et al. Group cognitive- behavioral therapy for generalized anxiety disorder: Treatment outcome and long-term follow-up. Journal of Consulting and Clinical Psychology. 2003; 71:821–5.
38. El Alaoui S, Hedman-Lagerlöf E, Lojotsson B, Lindefors N. Does internet-based cognitive behaviour therapy reduce healthcare costs and resource use in treatment of social anxiety disorder? A cost-minimisation analysis conducted alongside a randomised controlled trial. BMJ Open. 2017;7(9):e017053.
39. Ellard KK, Chronopoulos A. Cognitive behavioral therapy for anxiety disorders. In: Petersen, TJ, Sprich, SE, & Wilhelm, S. (Eds.). The Massachusetts General Hospital handbook of cognitive behavioral therapy. New York: Humana Press; 2016. p. 43–61.
40. Erickson DH. Group cognitive behavioural therapy for heterogeneous anxiety disorders. Cogn Behav Ther. 2003;32:179–86.
41. Fernandez MA, Short M. Wounded warriors with PTSD: a compilation of best practices and Technology in Treatment. TPC. 2014;4(2):114–21.
42. Feske U, Chambless DL. Cognitive behavioral versus exposure only treatment for social phobia: a meta-analysis. Behav Ther. 1995;26(4):695–720.

43. First MB, Williams JB. SCID-5-CV: structured clinical interview for DSM-5 disorders: clinician version. Arlington: American Psychiatric Association Publishing; 2016.
44. Foa EB, Franklin ME, Moser J. Context in the clinic: how well do cognitive-behavioral therapies and medications work in combination? Biol Psychiatry. 2002;52(10):987–97.
45. Foa EB, Kozak MJ. Emotional processing of fear: exposure to corrective information. Psychol Bull. 1986;99(1):20.
46. Freheit S, Vye C, Swan R, Cady M. Cognitive-behavioral therapy for anxiety: is dissemination working? Behav Ther. 2004;27:25–32.
47. Gaggioli A, Riva G. From mobile mental health to mobile wellbeing: opportunities and challenges. Stud Health Technol Inform. 2013;184:141–7.
48. Gersh E, Hallford D, Rice SM, Kazantzis N, Gersh H, Gersh B, Mccarty C. Systematic review and meta-analysis of dropout rates in individual psychotherapy for generalized anxiety disorder. J Anxiety Disord. 2017;52:25–33.
49. Goldin PR, Morrison A, Jazieri H, Brozovich F, Heimberg R, Gross J. Group CBT versus MBSR for social anxiety disorder: a randomized controlled trial. J Consult Clin Psychol. 2016;84(5):427–37.
50. Gould RA, Buckminster S, Pollack MH, Otto MW, Massachusetts LY. Cognitive behavioral and pharmacological treatment for social phobia: a meta-analysis. Clin Psychol Sci Pract. 1997;4(4):291–306.
51. Gould RA, Otto MW, Pollack MH, Yap L. Cognitive behavioral and pharmacological treatment of generalized anxiety disorder: a preliminary meta-analysis. Behav Ther. 1997;28(2):285–305.
52. Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, Dadds MR. A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. Biol Psychiatry. 2008;63(6):544–9.
53. Haby MM, Donnelly M, Corry J, Vos T. Cognitive behavioural therapy for depression, panic disorder and generalized anxiety disorder: a meta-regression of factors that may predict outcome. Aust N Z J Psychiatry. 2006;40(1):9–19.
54. Hall GC, Ibaraki AY, Huang ER, Marti CN, Stice E. A meta-analysis of cultural adaptations of psychological interventions. Behav Ther. 2016;47(6):993.
55. Heeren A, Reese HE, McNally RJ, Philippot P. Attention training toward and away from threat in social phobia: effects on subjective, behavioral, and physiological measures of anxiety. Behav Res Ther. 2012;50(1):30–9.
56. Heimberg RG. Cognitive-behavioral therapy for social anxiety disorder: current status and future directions. Biol Psychiatry. 2002;51(1):101–8.
57. Heimberg RG, Becker RE. Cognitive-behavioral group therapy for social phobia: basic mechanisms and clinical strategies. New York: Guilford Press; 2002.
58. Heimberg RG, Dodge CS, Hope DA, Kennedy CR, Zollo LJ, Becker RE. Cognitive behavioral group treatment for social phobia: comparison with a credible placebo control. Cogn Ther Res. 1990;14(1):1–23.
59. Heimberg RG, Liebowitz MR, Hope DA, Schneier FR, Holt CS, Welkowitz LA, et al. Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. Arch Gen Psychiatry. 1998;55(12):1133–41.
60. Herbert JD, Gaudiano BA, Rheingold AA, Myers VH, Dalrymple K, Nolan EM. Social skills training augments the effectiveness of cognitive behavioral group therapy for social anxiety disorder. Behav Ther. 2005;36(2):125–38.
61. Hipol LJ, Deacon BJ. Dissemination of evidence-based practices for anxiety disorders in Wyoming: a survey of practicing psychotherapists. Behav Modif. 2013;37(2):170–88.
62. Hofmann SG. Cognitive factors that maintain social anxiety disorder: a comprehensive model and its treatment implications. Cogn Behav Ther. 2007;36(4):193–209.
63. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cogn Ther Res. 2012;36(5):427–40.
64. Hofmann SG, Meuret AE, Smits JA, Simon NM, Pollack MH, Eisenmenger K, et al. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. Arch Gen Psychiatry. 2006;63(3):298–304.

65. Hofmann SG, Sawyer AT, Korte KJ, Smits JA. Is it beneficial to add pharmacotherapy to cognitive-behavioral therapy when treating anxiety disorders? A meta-analytic review. Int J Cogn Ther. 2009;2(2):160–75.

66. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry. 2008;69(4): 621–32.

67. Hofmann SG, Smits JA, Asnaani A, Gutner CA, Otto MW. Cognitive enhancers for anxiety disorders. Pharmacol Biochem Behav. 2011;99(2):275–84.

68. Hofmann SG, Wu JQ, Boettcher H. D-Cycloserine as an augmentation strategy for cognitive behavioral therapy of anxiety disorders. Biol Mood Anxiety Disord. 2013;3(1):11.

69. Hollon SD, Beck AT. Cognitive and cognitive behavioral therapies. In: Garfield SL, Bergin AE, editors. Handbook of psychotherapy and behavior change. New York: Wiley; 1994. p. 428–66.

70. Joyce T, Globe A, Moody C. Assessment of the component skills for cognitive therapy in adults with intellectual disability. J Appl Res Intellect Disabil. 2006;19:17–23.

71. Kazantzis N, Deane FP, Ronan KR. Homework assignments in cognitive and behavioral therapy: a meta analysis. Clin Psychol Sci Pract. 2000;7(2):189–202.

72. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602.

73. Klein EB, Stone WN, Hicks MW, Pritchard IL. Understanding dropouts. J Ment Health Couns. 2003;25(2):89–100.

74. Kobak KA, Wolitzky-Taylor K, Craske MG, Rose RD. Therapist training on cognitive behavior therapy for anxiety disorders using internet-based technologies. Cogn Ther Res. 2017;41(2):252–65.

75. Koch E, Spates R, Himle J. Comparison of behavioral and cognitive-behavioral one-session exposure treatments for small animal phobias. Behav Res Ther. 2004;42:1483–504.

76. Lazarov A, Marom S, Yahalom N, Pine DS, Hermesh H, Bar-Haim Y. Attention bias modification augments cognitive–behavioral group therapy for social anxiety disorder: a randomized controlled trial. Psychol Med. 2018;48(13):2177–85.

77. Ledgerwood L, Richardson R, Cranney J. Effects of D-cycloserine on extinction of conditioned freezing. Behav Neurosci. 2003;117(2):341.

78. Ledgerwood L, Richardson R, Cranney J. D-cycloserine and the facilitation of extinction of conditioned fear: consequences for reinstatement. Behav Neurosci. 2004;118(3):505.

79. MacLeod C, Rutherford E, Campbell L, Ebsworthy G, Holker L. Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. J Abnorm Psychol. 2002;111(1):107.

80. Marchand A, Coutu MF, Dupuis G, Fleet R, Borgeat F, Todorov C, Mainguy N. Treatment of panic disorder with agoraphobia: randomized placebo-controlled trial of four psychosocial treatments combined with imipramine or placebo. Cogn Behav Ther. 2008;37(3):146–59.

81. Marks IM, Kenwright M, McDonough M, Whittaker M, Mataix-Cols D. Saving clinicians' time by delegating routine aspects of therapy to a computer: a randomized controlled trial in phobia/panic disorder. Psychol Med. 2004;34(1):9–17.

82. Mathews A, MacLeod C. Discrimination of threat cues without awareness in anxiety states. J Abnorm Psychol. 1986;95(2):131.

83. McEvoy PM, Nathan P, Norton PJ. Efficacy of transdiagnostic treatments: a review of published outcome studies and future research directions. J Cogn Psychother. 2009;23:27–40.

84. Mineka S, Zinbarg R. A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. Am Psychol. 2006;61(1):10.

85. Miranda J, Green BL, Krupnick JL, Chung J, Siddique J, Belin T, Revicki D. Year outcomes of a randomized clinical trial treating depression in low-income minority women. J Consult Clin Psychol. 2006;74(1):99–11.

86. Mitte K. A meta-analysis of the efficacy of psycho-and pharmacotherapy in panic disorder with and without agoraphobia. J Affect Disord. 2005;88(1):27–45.

87. Mohlman J, Gorman JM. The role of executive functioning in CBT: a pilot study with anxious older adults. Behav Res Ther. 2005;43(4):447–65.

88. Mörtberg E, Karlsson A, Fyring C, Sundin O. Intensive cognitive-behavioral group treatment (CBGT) of social phobia: a randomized controlled study. J Anxiety Disord. 2006;20(5):646–60.

89. Morissette SB, Spiegel DA, Heinrichs N. Sensation-focused intensive treatment for panic disorder with moderate to severe agoraphobia. Cogn Behav Pract. 2005;12(1):17–29.

90. Mowrer O. Learning theory and behavior. Hoboken: Wiley; 1960.

91. Norton PJ. A randomized clinical trial of transdiagnostic CBT for anxiety disorder by comparison to relaxation training. Behav Ther. 2012;43(3):506–17.

92. Norton PJ, Barrera TL. Transdiagnostic versus diagnosis-specific cbt for anxiety disorders: a preliminary randomized controlled noninferiority trial. Depress Anxiety. 2012;29(10):874–82.

93. Norton PJ, Price EC. A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. J Nerv Ment Dis. 2007;195(6):521–31.

94. Oathamshaw S, Haddock G. Do people with intellectual disabilities and psychosis have the cognitive skills required to undertake cognitive Behavioural therapy? J Appl Res Intellect Disabil. 2006;19:35–46.

95. Ost LG, Alm T, Brandberg M, Breitholtz E. One vs five sessions of exposure and five sessions of cognitive therapy in the treatment of claustrophobia. Behav Res Ther. 2001;39(2):167–83.

96. Ost LG, Brandberg M, Alm T. One versus five sessions of exposure in the treatment of flying phobia. Behav Res Ther. 1997;35(11):987–96.

97. Otte C. Cognitive behavioral therapy in anxiety disorders: current state of the evidence. Dialogues Clin Neurosci. 2011;13(4):413–21.

98. Otto MW. Stories and metaphors in cognitive-behavior therapy. Cogn Behav Pract. 2000;7(2):166–72.

99. Otto MW, Pollack MH, Meltzer-Brody S, Rosenbaum JF. Cognitive-behavioral therapy for benzodiazepine discontinuation in panic disorder patients. Psychopharmacol Bull. 1992;28(2):123–30.

100. Otto MW, Tolin DF, Simon NM, Pearlson GD, Basden S, Meunier SA, et al. Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. Biol Psychiatry. 2010;67(4):365–70.

101. Ougrin D. Efficacy of exposure versus cognitive therapy in anxiety disorders: systematic review and meta-analysis. BMC Psychiatry. 2011;11:200.

102. Peris TS, Compton SN, Kendall PC, Birmaher B, Sherrill J, March J, et al. Trajectories of change in youth anxiety during cognitive—behavior therapy. J Consult Clin Psychol. 2015;83(2):239.

103. Prentice J, Dobson K. A review of the risks and benefits associated with mobile phone applications for psychological interventions. Can Psychol. 2014;55(4):282–90.

104. Proudfoot J, Goldberg D, Mann A, Everitt B, Marks I, Gray JA. Computerized, interactive, multimedia cognitive-behavioural program for anxiety and depression in general practice. Psychol Med. 2003;33(2):217–27.

105. Rapee RM, MacLeod C, Carpenter L, Gaston JE, Frei J, Peters L, Baillie AJ. Integrating cognitive bias modification into a standard cognitive behavioural treatment package for social phobia: a randomized controlled trial. Behav Res Ther. 2013;51(4–5):207–15.

106. Rentz TO, Powers MB, Smits JA, Cougle JR, Telch MJ. Active-imaginal exposure: examination of a new behavioral treatment for cynophobia (dog phobia). Behav Res Ther. 2003;41(11):1337–53.

107. Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinctionof fear. Arch Gen Psychiatry. 2004;61(11):1136–44.

108. Rodebaugh TL, Holaway RM, Heimberg RG. The treatment of social anxiety disorder. Clin Psychol Rev. 2004;24(7):883–908.

109. Roemer L, Orsillo SM. Mindfulness-and acceptance-based behavioral therapies in practice. New York: Guilford Press; 2010.

110. Rothbaum BO, Hodges L, Smith S, Lee JH, Price L. A controlled study of virtual reality exposure therapy for the fear of flying. J Consult Clin Psychol. 2000;68(6):1020–6.
111. Salkovskis PM, Clark DM, Hackmann A. Treatment of panic attacks using cognitive therapy without exposure or breathing retraining. Behav Res Ther. 1991;29(2):161–6.
112. Salkovskis PM, Hackmann A, Wells A, Gelder MG, Clark DM. Belief disconfirmation versus habituation approaches to situational exposure in panic disorder with agoraphobia: a pilot study. Behav Res Ther. 2007;45(5):877–85.
113. Sanderson WC, Raue PJ, Wetzler S. The generalizability of cognitive behavior therapy for panic disorder. J Cogn Psychother. 1998;12(4):323.
114. Schmidt NB, Richey JA, Buckner JD, Timpano KR. Attention training for generalized social anxiety disorder. J Abnorm Psychol. 2009;118(1):5.
115. Sharp DM, Power KG, Swanson V. A comparison of the efficacy and acceptability of group versus individual cognitive behaviour therapy in the treatment of panic disorder and agoraphobia in primary care. Clin Psychol Psychother. 2004;11(2):73–82.
116. Sholomskas DE, Carroll KM. One small step for manuals: computer-assisted training in twelve-step facilitation. J Stud Alcohol Drugs. 2006;67(6):939–45.
117. Siegmund A, Golfels F, Finck C, Halisch A, Räth D, Plag J, Ströhle A. D-cycloserine does not improve but might slightly speed up the outcome of in-vivo exposure therapy in patients with severe agoraphobia and panic disorder in a randomized double blind clinical trial. J Psychiatr Res. 2011;45(8):1042–7.
118. Sloan T, Telch MJ. The effects of safety-seeking behavior and guided threat reappraisal on fear reduction during exposure: an experimental investigation. Behav Res Ther. 2002;40(3):235–51.
119. Smits JA, Rosenfield D, Otto MW, Powers MB, Hofmann SG, Telch MJ, Pollack MH, Tart CD. D- cycloserine enhancement of fear extinction is specific to successful exposure sessions: Evidence from the treatment of height phobia. Biological Psychiatry. 2013;73:1054–8.
120. Spek V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med. 2006;37(3):319–28.
121. Sokol L, Beck AT, Greenberg RL, et al. Cognitive therapy of panic disorder: a non-pharmacological alternative. J Nerv Ment Dis. 1989;177:711–6.
122. Sprich SE, Olatunji BO, Reese HE, Otto MW, Rosenfield E, Wilhelm S. Cognitive-behavioral therapy, behavioral therapy, and cognitive therapy. In: Stern TA, Fava M, Rosenbaum JF, Wilens TE, editors. Massachusetts General Hospital comprehensive clinical psychiatry. Elsevier Health Sciences; 2016. p. 152–64.
123. Stewart RE, Chambless DL. Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: a meta-analysis of effectiveness studies. J Consult Clin Psychol. 2009;77(4):595–606.
124. Swift JK, Greenberg RP. A treatment by disorder Meta-analysis of dropout from psychotherapy. J Psychother Integr. 2014;24(3):193–207.
125. Tart CD, Handelsman PR, DeBoer LB, Rosenfield D, Pollack MH, Hofmann SG, et al. Augmentation of exposure therapy with post-session administration of D-cycloserine. J Psychiatr Res. 2013;47(2):168–74.
126. Taylor S. Meta-analysis of cognitive-behavioral treatments for social phobia. J Behav Ther Exp Psychiatry. 1996;27(1):1–9.
127. Taylor S, Abramowitz JS, McKay D. Non-adherence and non-response in the treatment of anxiety disorders. J Anxiety Disord. 2012;26(5):583–9.
128. Thorpe SJ, Salkovskis PM. Phobic beliefs: do cognitive factors play a role in specific phobias? Behav Res Ther. 1995;33(7):805–16.
129. Van Balkom AJ, Bakker A, Spinhoven P, Blaauw BM, Smeenk S, Ruesink B. A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. J Nerv Ment Dis. 1997;185(8):510–6.

130. Van Ballegooiien W, Cuijpers P, van Straten A, Karyotaki E, Andersson G, Smit JH, Riper H. Adherence to internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. PLoS One. 2014;9(7):e100674.
131. Van Gerwen LJ, Spinhoven P, Diekstra RFW, Van Dyck R. Multicomponent standardized treatment programs for fear of flying: description and effectiveness. Cogn Behav Pract. 2002;9(2):138–49.
132. Vansteenwegen D, Vervliet B, Iberico C, Baeyens F, Van den Bergh O, Hermans D. The repeated confrontation with videotapes of spiders in multiple contexts attenuates renewal of fear in spider-anxious students. Behav Res Ther. 2007;45(6):1169–79.
133. Walker DL, Ressler KJ, Lu KT, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci. 2002;22(6):2343–51.
134. Weiss BJ, Singh S, Hope DA. Cognitive-behavioral therapy for immigrants presenting with social anxiety disorder: two case studies. Clin Case Stud. 2011;10(4):324–42.
135. Whitfield G, Williams C. If the evidence is so good – why doesn't anyone use them? – a national survey of the use of computerized cognitive behaviour therapy. Behav Cogn Psychother. 2004;32:57–65.
136. Williams SL, Falbo J. Cognitive and performance-based treatments for panic attacks in people with varying degrees of agoraphobic disability. Behav Res Ther. 1996;34(3):253–64.
137. Willner P, Jones J, Tams R, Green G. A randomized controlled trial of the efficacy of a cognitive-Behavioural anger Management Group for Clients with learning disabilities. J Appl Res Intellect Disabil. 2002;15:224–35.
138. Wolitzky-Taylor KB, Horowitz JD, Powers MB, Telch MJ. Psychological approaches in the treatment of specific phobias: a meta-analysis. Clin Psychol Rev. 2008;28(6):1021–37.
139. Wolpe J. Psychotherapy by reciprocal inhibition. Stanford: Stanford University Press; 1958.
140. Wright JH. Cognitive behavior therapy: Basic principles and recent advances. Focus. 2006;4(2):173–8.
141. Zandberg LJ, Wilson GT. Train-the-trainer: implementation of cognitive behavioral guided self-help for recurrent binge eating in a naturalistic setting. Eur Eat Disord Rev. 2013;21(3):230–7.
142. Zinbarg RE, Craske MG, Barlow DH. Mastery of your anxiety and worry (MAW): therapist guide. Oxford/New York: Oxford University Press; 2006.

Chapter 13
Psychopharmacology of Anxiety Disorders

Andrew Melaragno, Vincenza Spera, and Eric Bui

Introduction

Anxiety disorders are frequent conditions associated with significant distress and dysfunction. In this chapter, we will start by briefly reviewing how we currently understand the neurobiological underpinnings of anxiety disorders. We will then go on to discuss some general principles which are useful for treating anxiety disorders with psychotropic medications. Finally, the remainder of this chapter will review the classes of medications and specific agents indicated for panic disorder (PD), generalized anxiety disorder (GAD), and social anxiety disorder (SAD).

Neurobiology of Anxiety Disorders

The neurocircuitry of anxiety disorders is described in detail in Chap. 2. While our understanding of the underlying neuroanatomy and brain circuitry involved in various anxiety disorders has expanded over the years, much remains to be elucidated. Much of this understanding has been gained through behavioral models in animals and functional neuroimaging studies that correlate the metabolic activity of areas of the brain to the activation of specific emotional and cognitive pathways. One of the main hypotheses to explain the disrupted brain activity in anxiety disorders (espe-

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cially PD and SAD, but also GAD) suggests dysregulation in the "fear circuit," where there is an imbalance of signaling between an overactive limbic system and underactive frontal cortical areas [47].

Dysfunction or dysregulation of certain central neurotransmitter systems including serotonin, norepinephrine, and gamma aminobutyric acid (GABA) has been suggested to underlie the pathophysiology of anxiety disorders [12, 19, 34, 41, 59] and may thus explain how different pharmacologic agents are efficacious in reducing anxiety symptom severity. A number of studies suggest that dysfunction of the serotoninergic system may be associated with anxiety disorders [22, 43]. For example, one study discovered a relative decrease in density of paroxetine binding sites on platelets (a proxy for density of serotonin transporters and thus serotonergic transmission) in patients with anxiety disorders relative to normal controls. Similarly, research suggests a potential role of norepinephrine in anxiety disorders. An early study reported that the stimulation of the locus coeruleus, a small region dense in norepinephrinergic neurons, may increase anxiety [42]. Further, other research reported abnormalities in central pre- and postsynaptic alpha-2 adrenergic receptors in individuals with anxiety disorders [1]. Finally, dysfunction in the inhibitory GABA system might also be implicated in the pathophysiology of anxiety disorders. A high density of GABA receptors in brain regions relevant for fear and anxiety such as the amygdala and hippocampus have thus been reported [10]. Selective serotonin reuptake inhibitor antidepressants (SSRIs) are believed to exert their anxiolytic action through modulation of the serotonin system, while monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCA), and serotonin and norepinephrine reuptake inhibitors (SNRIs) are thought to exert their anxiolytic action through modulation of both the serotonin and the norepinephrine system. Benzodiazepines are believed to have an immediate action on GABA receptors.

General Principles of Pharmacotherapy Approaches to Anxiety Disorders

First-line pharmacologic treatment for all anxiety disorders are antidepressants, including SSRIs and SNRIs, as well as less commonly used but comparably effective TCAs and MAOIs. When prescribing an antidepressant medication for anxiety, it is important to let the patient know that 4–8 weeks of treatment are typically needed to see the full effect of any given dose. Partial responses may be seen earlier but typically on the order of weeks, not days. Furthermore, because patients with anxiety disorders tend to experience increased perceived side effects to medications and frequent somatic symptoms, they may be particularly sensitive to the initiation side effects. There is thus some evidence that patients with PD and GAD may be more attuned to physiological changes (elevated anxiety sensitivity) [30] and thus perceive subtle changes in their bodies in response to medication more intensely and adversely. For this reason, the recommended titration schedules for patients with increased anxiety sensitivity [2, 5, 8], including those with full-blown or subthreshold PD, generally start lower (i.e., half dose) and proceed more slowly upward

compared to treating depression [27]. For instance, whereas the starting dose of sertraline may be 50 mg daily for depression, patients with anxiety usually benefit from starting at 25 mg. Although common in practice, the foregoing management has not been systematically studied [50]. Finally, treatment response and remission may also require higher doses compared to those used for treating depression.

When a patient completes an adequate therapeutic trial of a first-line agent with only an absent to partial response, no consensus algorithm exists to guide the next steps in pharmacologic treatment. Therapeutic options after one or multiple failed trials with SSRIs/SNRIs include adding an adjunctive treatment, switching to another SSRI/SNRI or switching to another class such as a TCA or an MAOI (Table 13.1).

Table 13.1 FDA-approved medications for anxiety disorders

Medication (brand) No generic available	Available PO dosage forms	Starting dosage (mg/day)	Target dose range (mg)	FDA-approved indications	Specific notes
Selective serotonin reuptake inhibitors					
Escitalopram (Lexapro)	5, 10, 20 mg tablets; 5 mg/5 ml solution	5–10	10–30	*GAD*	Few drug interactions
Sertraline (Zoloft)	25, 50, 100 mg tablets	25	50–200	*PD, SAD, PTSD*	Few drug interactions
Fluoxetine (Prozac)	10, 20, 40 mg capsules; 10, 20, 60 mg tablets; 90 mg weekly delayed-release capsules (equivalent to 20 mg/d); 20 mg/5 mL solution	10	20–80	*PD*	Very long elimination half-life CYP2D6 strong inhibitor Least weight gain Anecdotally more often activating
Paroxetine (Paxil)	10, 20, 30, 40 mg tablets; 7.5 mg capsules; 10 mg/5 mL solution	10	20–60	*PD, GAD, SAD, PTSD*	Anticholinergic and antihistaminergic side effects: sedation, dry mouth, weight gain Strong CYP2D6 inhibitor Difficult discontinuation – taper slowly
Paroxetine CR (Paxil CR)	12.5, 25, 37.5 mg tablets	12.5	25–75	*PD, GAD, SAD, PTSD*	Same as paroxetine

(continued)

Table 13.1 (continued)

Medication (brand) No generic available	Available PO dosage forms	Starting dosage (mg/day)	Target dose range (mg)	FDA-approved indications	Specific notes
Fluvoxamine (Luvox)	25, 50, 100 mg tablets; 100, 150 mg ER capsules	25	100–300	*SAD*	Many drug interactions CYP1A2 strong inhibitor – inhibits own metabolism, increases serum levels of clozapine, caffeine
SNRIs					
Venlafaxine XR (Effexor XR)	37.5, 75, 150 mg capsules; 37.5, 75, 150, 225 mg ER tablets (generic only, not FDA approved)	37.5	75–300	*PD*, *GAD*, *SAD*	Monitor BP for patients at doses ≥225 mg/day Difficult discontinuation – taper slowly
Duloxetine (Cymbalta)	20, 30, 40, 60 mg delayed-release capsules	20	30–90	*GAD*	FDA-approved for fibromyalgia and chronic pain
Azapirones					
Buspirone (Buspar)	5, 7.5, 10, 15, 30 mg tablets	5 BID – TID	10–20 BID – TID	*GAD*	No efficacy as monotherapy except in GAD
Benzodiazepines					
Lorazepam (Ativan)	0.5, 1, 2 mg tabs; 2 mg/1 mL solution	0.5 QD – TID	0.5–2 QD – TID	*"Anxiety disorders"*	
Clonazepam (Klonopin)	0.5, 1, 2 mg tabs; 0.125, 0.25, 0.5, 1, 2 mg ODT	0.25–0.5 BID	0.5–1 BID (max 4 daily)	*PD*	No proven increase efficacy advantage but increased side effects at doses >2 mg/day

Notes: The SSRI citalopram do not have FDA approval for any anxiety disorders but some efficacy data exist.

Specific Medications and Drug Classes Used in the Treatment of Anxiety Disorders

Selective Serotonin Reuptake Inhibitor (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

SSRIs and SNRIs are favored as first-line medications based on their broad spectrum of efficacy that can target multiple anxiety disorders as well as depression at the same time, their favorable side effect profile compared to older antidepressants, and a lack of risk of abuse and dependence compared to the benzodiazepines [4].

SSRIs and SNRIs are generally well tolerated, and severe adverse events are exceedingly rare. The common side effects of SSRIS/SNRIs are best separated into short-term adverse effects, which present on initiation and with dose increases, and usually remit within 1–3 weeks on a steady dose, and long-term adverse effects, which become evident weeks to months into treatment and do not fade over time. The most common short-term adverse effects are gastrointestinal, including dyspepsia, nausea, and loose stools. Patients may also experience activating side effects, which include motor restlessness, temporarily increased anxiety symptoms, and insomnia. Other typical short-term adverse effects include drowsiness and headaches.

The most common (and problematic) of the persistent adverse effects of antidepressants is sexual dysfunction. This can include diminished sexual desire and delay in or inability to achieve orgasm in both sexes, as well as erectile dysfunction in men. When sexual side effects emerge, they can have a major impact on patients' quality of life, medication adherence, and ability to tolerate an adequate dose for remission of symptoms [44]. Their prevalence is likely underestimated due to underreporting but has been estimated to range from 30% to 75% for SSRIs and SNRIs [14, 25, 26]. The usual strategies for managing adverse sexual effects include dose reduction, switching to a different SSRI/SNRI, or adding another drug to counteract the sexual dysfunction (although insufficient evidence is available to support any of the many drugs used as augmenting agents for sexual dysfunction) [55].

Another important sustained adverse effect of SSRIs is increased bleeding risk, which is imparted by the role of serotonin in inhibiting platelet aggregation. This is usually of minimal significance but may lead to clinically increased risk of bleeding if patients are simultaneously prescribed SSRIs/SNRIs with antiplatelet drugs such as aspirin and clopidogrel, or anticoagulants such as warfarin or the direct oral anticoagulants rivaroxaban, apixaban, and dabigatran.

Hyponatremia has been reported in association with SSRIs/SNRIs, usually caused by pathologic release of antidiuretic hormone from the hypothalamus, which leads to free water retention and dilution of serum sodium levels. The most feared of adverse effects is serotonin syndrome, which can occur if these drugs are coprescribed with other medications that act on serotonin receptors or increase levels of serotonin in the brain and body (i.e., other antidepressants, especially MAOIs,

certain antibiotics such as linezolid, pain medications such as tramadol and meperidine, illicit drugs such as MDMA and cocaine, and some herbal remedies such as St. John's wort). Serotonin syndrome is a clinical syndrome that falls along a spectrum of severity, but in its most recognizable and fulminant form, it may include some or all of high fever and altered mental status which may include agitation, sweating, tremor, hyperreflexia and clonus, myoclonus, dilated pupils, and diarrhea. The main treatment is promptly recognizing and removing all serotonin-modulating agents.

One of the most controversial "side effects" of the use of SSRIs is the association that has been observed between SSRIs and a slight increased incidence of suicidal ideation and behavior in younger patients across randomized controlled trials. This has led to the addition of a "black box warning" by the U.S. Food and Drug Administration (FDA) in 2004 regarding increased risk of suicidal ideation and behavior (attempts) with SSRI/SNRI therapy in children and adolescents, which was extended in 2006 to include the population of young adults from 18 to 24 years. A proposed mechanism for the connection with suicidal behavior is that the activating effects of antidepressants precede relief of symptoms of the underlying disorder, leaving patients who have already contemplated suicide or self-harm with more energy and motivation to engage in such action. Reviews in adult populations aged 25 and older have failed to find an increased rate of completed suicides in patients on antidepressants compared to placebo [53]. Consensus opinions on this topic have noted that risk–benefit analysis favors the use of antidepressants, because untreated depression and anxiety place people at higher risk of suicide [17, 48]. However, response to antidepressants in any individual patient is unpredictable, and thus patients should be closely monitored, especially during initiation of treatment.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have demonstrated efficacy in the treatment of PD and were widely used for this indication before the arrival of SSRIs, SNRIs, and benzodiazepines. Imipramine (the prototypical TCA) has the strongest and most randomized controlled trial evidence, but studies have also shown efficacy for clomipramine – possibly superior to imipramine [32] – and preliminary evidence for desipramine [23, 45]. Though they are generally as efficacious as newer antidepressant medications, TCAs are used less often most importantly due to risk of lethality in overdose caused by fatal cardiac arrhythmias and anticholinergic poisoning. Another reason TCAs have fallen out of favor is a broad side effect burden caused by their effects on numerous drug receptors, which includes anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision, tachycardia and cognitive effects), with other side effects including sedation, orthostatic hypotension, weight gain, and cardiac conduction problems. This has led to a high dropout rate of between 30% and 70% in most RCTs [3, 28]. Another factor that has favored newer

medications over TCAs is that the available evidence base supports TCAs in a narrower range of anxiety disorders when compared to SSRIs/SNRIs and benzodiazepines. TCAs have failed to show comparable efficacy to SSRIs/SNRIs for the treatment of SAD. For GAD, imipramine has trials supporting it as comparable in efficacy to both SSRIs and benzodiazepines, but with greater side effect burden than the former and slower onset of effect than the latter.

Monoamine Oxidase Inhibitors

The MAOIs (particularly phenelzine and tranylcypromine) were once considered the treatment of choice for pharmacologic treatment of SAD based on evidence of strong efficacy in randomized controlled trials, until they were overtaken by the SSRIs and SNRIs. Often intolerable side effects and an unfavorable safety profile are the major reasons why MAOIs were largely replaced by SSRIs and SNRIs for treatment of this disorder [9]. Common MAOI side effects include orthostatic hypotension, paresthesia, weight gain, and sexual dysfunction. Unlike those who take newer agents, patients taking MAOIs also need to strictly adhere to dietary restrictions disallowing foods such as aged cheeses and beers which contain tyramine that, in sufficient amounts, can interact with MAOIs and lead to fatal hypertensive crises. Furthermore, drug interactions with MAOIs are a significant safety concern. Taking other drugs that affect serotonin, norepinephrine, and dopamine, or their associated receptors, in conjunction with MAOIs may precipitate serotonin syndrome or dangerous hypertension [57].

Beta Blockers

Beta-adrenergic blockers are a class of medications which are usually prescribed as antihypertensive and heart failure drugs but have also been used off-label as sympatholytic agents to manage short-term anxiety reactions about specific events [20]. Beta-blockers have not been shown to decrease psychological anxiety; however, they can decrease the intensity of physical anxiety manifestations, which might serve to reduce the secondary anxiety about others perceiving and judging physical signs of nervousness. As such they have been used for performance anxiety [13]. The usual agent is propranolol 10–40 mg given 30 minutes to 1 hour before the performance situation. A reasonable approach for finding the right dose is measuring resting heart rate at the time of peak effect (~1 hour) and titrating the dose to a resting heart rate of roughly 60 beats per minute. Higher doses have been studied but have been associated with greater incidence of adverse effects. The duration of effect is short, on the order of a few hours. Atenolol has also been demonstrated to be helpful for this purpose but is used less commonly. Propranolol has a theoretical benefit of readily crossing the blood–brain barrier, although its anxiolytic effect is

thought to be mostly mediated by its peripheral sympathetic nervous system blocking effects. Adverse effects may include lightheadedness, bradycardia, and hypotension. Caution should be used for patients with significant obstructive lung disease (asthma or chronic obstructive pulmonary disease), as blockade of the beta-2 receptor causes bronchoconstriction.

Benzodiazepines

Benzodiazepines are a very effective class of medications for treatment of the immediate symptoms of anxiety and, in select cases, for long-term suppression of panic attacks and management of the symptoms of SAD and GAD. These medications continue to be widely prescribed, although over the last several decades considerable controversy has arisen due to concerns about potential for misuse and long-term dependence even among those using them appropriately, long-term cognitive effects, and potential for fatal respiratory depression when used in combination with opioids, alcohol, or other sedating drugs [7, 15].

While an approach that combines medication with cognitive behavioral therapy (CBT; see Chap. 12) may produce the most successful treatment outcomes, over-reliance on PRN anxiolytics, particularly fast-acting benzodiazepines, can interfere with engagement and successful unlearning of avoidant behaviors that perpetuate anxiety. Taking a powerful and fast acting anxiety quelling medication can be considered an avoidance behavior, even if it used to enable a person to face an anxiety inducing stimulus, because they will be prevented from feeling the associated anxiety and then extinguishing that same anxiety through repeated exposures. Thus, if used in an inappropriate fashion by a patient who is also engaged in CBT, benzodiazepines may undermine the very mechanism by which the psychotherapy works [35, 36].

In terms of adverse effects, benzodiazepines on their own are generally very well tolerated but can cause sedation, dizziness, gait problems, and cognitive slowing [56]. Tolerance tends to develop to the sedating/hypnotic effects of the drugs, but when used properly their anxiolytic benefits should be sustained, and studies have not demonstrated a consistent pattern of dose escalation over time. However, they can be associated with chemical dependence, meaning when they are stopped or reduced significantly, the patient may notice "rebound" symptoms, including a worsening of underlying anxiety and insomnia. Abrupt cessation of benzodiazepines from high doses can lead to a life-threatening withdrawal syndrome which may include alterations in consciousness or confusion, seizures, and hemodynamic instability [51]. Agents with longer clearance half-lives such as clonazepam and diazepam carry less risk of life-threatening withdrawal than agents with short half-lives such as alprazolam.

Patients who misuse or abuse benzodiazepines usually have abused other substances as well. Thus, they should not be started in anyone with a substantial history of substance abuse.

One of the most common uses of benzodiazepines in anxiety disorders is for short-term relief of anxiety during initiation and titration of an antidepressant. This can be especially useful to counteract the activating effects which often present in patients with anxiety starting SSRI/SNRI therapy, and to temporize anxiety symptoms during the prolonged interval required for the antidepressants to demonstrate a therapeutic effect [18]. There is no consensus on whether benzodiazepines used in this fashion should be given on a standing or as-needed (PRN) basis. Factors favoring standing dosage include more controlled drug exposure throughout the day and less behavioral reinforcement from pill taking. More sparing use of PRN medication poses less risk of physical dependence in longer-term use and would be appropriate especially in the more transitory situational anxiety. In the case of prescribing standing benzodiazepines, a long-acting medication should be used such as clonazepam, which can be dosed twice daily or sometimes daily [39]. In either case, the lowest dose required to achieve a therapeutic effect should be employed, and the length of therapy should be relatively brief (a few weeks to about 2 months), especially if used in a standing fashion or if the patient ends up using PRN meds on a daily or almost daily basis. The benzodiazepine should be tapered over the course of at least a few weeks to avoid rebound anxiety and withdrawal symptoms. The longer a patient has been regularly taking benzodiazepines, the longer the planned taper should be in order to reduce associated discomfort.

In the right patient, long-term/indefinite use of benzodiazepines may indeed be appropriate. For instance, many patients suffer from disabling residual symptoms despite multiple adequate trials of first-line agents (SSRIs/SNRIs) and psychotherapy. Furthermore, since patients with anxiety disorders often require higher doses of antidepressant to fully remit, they may be limited from titrating these drugs to the maximally effective dose by problematic adverse effects such as sexual dysfunction. In these case, relatively low doses of benzodiazepines may help them achieve full remission as an augmenting agent [40, 46].

Other Agents

Buspirone

Buspirone (Buspar) is an agent that has moderate evidence from randomized controlled trials of being helpful for GAD, either as a monotherapy or as an adjunct to other first-line treatments. Although the exact mechanism of buspirone's anxiolytic effect is unclear, it is thought to be mediated by its agonist activity at 5HT-1A receptors as well as mild antagonism at D2 receptors. Advantages to this medication include minimal long-term side effect burden, notably no significant sexual side effects. Like SSRIs/SNRIs, buspirone has a delayed onset of anxiolytic effect. Unlike the antidepressants, buspirone is not effective as a monotherapy for depression, PD, or SAD and has very sparse evidence for its use as an adjunct in these

disorders. Typical effective dosing ranges from 20 to 30 mg total daily but can be as high as 60 mg.

Anticonvulsants

Pregabalin (*Lyrica*) has numerous randomized controlled trials supporting its efficacy in GAD [6] and has an official indication for use in GAD in the European Union, but not in the USA. As with duloxetine, this medication would be a good choice for patients with comorbid chronic pain syndromes such as fibromyalgia. Pregabalin is an anticonvulsant medication categorized as a GABA analog but does not achieve anxiolytic effects via action on GABA receptors. Rather, its proposed mechanism of action is via binding to the alpha-2-delta subunit of voltage-gated calcium channels on neurons in the central nervous system, leading to an overall inhibitory downstream effect. Commonly observed side effects include sedation, dizziness, headache, fatigue, visual changes, dry mouth, weight gain, and peripheral edema. Gabapentin, a drug closely related to pregabalin, is often used for GAD and other anxiety disorders, although there is limited randomized controlled trial data to support its use, except in SAD. The available evidence suggests high doses are needed for efficacy. In a key study showing benefit of gabapentin for SAD, more than 60% of the patients who achieved a positive response took the maximum daily dose of 3600 mg [37]. Pregabalin and gabapentin are C-5-controlled substances regulated by the U.S. Drug Enforcement Administration because of some abuse potential, although the risk is thought to be much lower than for benzodiazepines.

Antipsychotics

The efficacy of antipsychotic agents has also been studied with regard to treating anxiety. The typical antipsychotic trifluoperazine was unique in receiving an FDA indication for the treatment of nonpsychotic anxiety in doses ranging from 2 to 6 mg/day. Thioridazine had significant evidence for use in GAD but was withdrawn from the market worldwide due to excessive risk of cardiac arrhythmias. Quetiapine has numerous trials supporting its efficacy as a monotherapy in GAD, particularly at total daily doses of 150 mg or higher [24, 31]. Quetiapine may prove especially useful in a population with comorbid bipolar disorder and GAD, given the drug's demonstrated antimanic properties and efficacy in the prevention and acute treatment of bipolar depression [16, 54]. Despite abundant evidence of anxiolytic efficacy of neuroleptics, their adoption has been limited by concerns about the development of extrapyramidal symptoms and tardive dyskinesia in the case of first-generation drugs and weight gain and metabolic dysfunction in the case of second-generation drugs. Thus, antipsychotics should be reserved for patients with the most refractory anxiety, and prescribers should extensively counsel patients about the attendant risks and benefits.

Psychopharmacologic Approach to Specific Anxiety Disorders

Panic Disorder

Panic disorder is a syndrome marked by anxiety and pathological avoidance related to recurrent panic attacks, which are short-lived episodes of intense fear accompanied by very uncomfortable physical symptoms. At least some of the panic attacks must have occurred without a specific trigger. Patients may avoid a variety of situations they have mentally associated with the onset of panic attacks, and thus the avoidance may generalize to multiple important domains of life and significantly impair functioning. Treatment is focused first on reducing frequency and severity of panic attacks and, in the longer term, undoing patterns of learned avoidant behavior. Although some patients may attain full remission with psychotherapy with or without medication, for many, PD remains a relapsing–remitting chronic disorder for which the symptomatology varies considerably throughout time. Patients may be able to taper off medications slowly after a period of at least a year of sustained remission on a stable dose, and may maintain remission after cessation of pharmacotherapy. However, for many, indefinite treatment with medications may be needed.

Several SSRIs/SNRIs have FDA indications for panic disorder, including the SSRIs fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil/Paxil CR) and the SNRI venlafaxine (Effexor, extended release formulation only). However, the effectiveness of other agents has been demonstrated in multiple randomized controlled trials, including escitalopram (Lexapro), citalopram (Celexa), and fluvoxamine (Luvox) among the SSRIs. Duloxetine (Cymbalta) has preliminary evidence only at this time [49] but theoretically should be similarly effective given the demonstrated efficacy of the similar SNRI venlafaxine. Prescribing duloxetine for PD would be a reasonable choice in patients with comorbid chronic musculoskeletal pain, diabetic neuropathic pain, or fibromyalgia, as it carries the FDA indication for these conditions. As stated previously, patients with panic disorder are particularly sensitive to the activating effects or "jitteriness" associated with starting and up-titrating antidepressants, so low doses with slower titration are essential. Recommended starting doses per day are about half of those used in depression: 25 mg for sertraline, 10 mg for fluoxetine, 10 mg/12.5 mg for paroxetine/paroxetine CR, 37.5 mg for venlafaxine XR, 5 mg for escitalopram, 10 mg for citalopram, and 50 mg for fluvoxamine. Sometimes patients may even benefit from starting at half of the above doses.

Benzodiazepines are highly effective medications for the short-term treatment of panic attacks and valuable because of their relatively rapid onset of anxiolytic effect compared to antidepressants, as well as their favorable adverse effect profile compared to other second- and third-line agents, such as tricyclic antidepressants and MAOIs. However, as mentioned before, for patients engaged in CBT – which is the psychotherapeutic modality with the strongest evidence base for panic disorder – benzodiazepines may interfere with the essential process of learning that the physi-

ological symptoms of panic are safe. It follows that scheduled dosing is generally preferred in the use of benzodiazepines for panic disorder. Among the benzodiazepines, clonazepam has the most evidence for efficacy in PD. This medication has been shown to be well-tolerated and have sustained efficacy without significant dose escalation with long-term use [21, 33]. The dose may occasionally be given once daily at night or in the morning, but typically twice-daily dosing is best: The typical starting dose is 0.5–1 mg per day of clonazepam, and the studied therapeutic dosing range is 1–4 mg daily, but doses greater than 2 mg have been associated with higher rates of adverse effects. Lorazepam and diazepam have been studied and used to good effect in anxiety disorders including panic disorder, but do not carry specific indications for this use and require more frequent dosing due to their short duration of action (usually TID to QID). Alprazolam (Xanax, Xanax XR) is the other medication with FDA approval specific to PD. Due to its very rapid onset of effect and short duration of action, alprazolam is very effective as an acute abortive agent for panic attacks. However, the aforementioned pharmacokinetic properties can also produce a euphoric effect that is highly reinforcing and more conducive to misuse and abuse. If used on a standing basis, the short half-life and duration of action of alprazolam necessitate dosing it three to four times per day, and treatment may still be complicated by inter-dose anxiety or rebound symptoms. Alprazolam XR (Xanax XR) is an extended-release version of the drug with a smoother onset of action which can be dosed twice or sometimes once a day, similarly to clonazepam. Nevertheless, this medication is infrequently used in clinical practice.

There are number of other second-, third-, and fourth-line agents which have evidence for efficacy in PD, including TCAs, MAOIs, atypical antidepressants, anticonvulsants, and some second-generation antipsychotics (preliminary or mixed evidence), but if these drugs are being considered, the patient should be referred to a board-certified psychiatrist. TCAs, particularly clomipramine and imipramine, have been shown to be quite effective as treatments for panic disorder. Their use is limited by toxicity in overdose (usually secondary to lethal cardiac arrhythmias) even in relatively small amounts and a broad and problematic side effect profile which includes significant sedation, dry mouth, urinary retention, orthostatic hypotension, cardiac effects, and weight gain. Phenelzine, a hydrazine MAOI, has the strongest evidence among this class of drugs for efficacy in PD.

Social Anxiety Disorder

SAD is marked by recurrent disproportionate fear of social situations in which a person anticipates scrutiny from others, leading them to either avoid the distressing situations or to endure them with severe anxiety symptoms.

The pharmacological treatment of SAD aims to reduce anticipatory anxiety and distress, as well as avoidance behavior associated with social interaction and

performance situations. The most effective medications for social anxiety are antidepressants, benzodiazepines, and, in the case of performance-only anxiety, beta-adrenergic blockers. Other medications including anticonvulsants and MAOIs have been studied and shown to be effective in this population, but this chapter will primarily focus only on the aforementioned first-line drugs.

Sertraline, paroxetine (both regular and CR formulations), and venlafaxine carry FDA indications for use in SAD among the first-line treatments of SSRIs and SNRIs. Empirical data also support the use of escitalopram, citalopram, and fluvoxamine for SAD. All of these SSRIs/SNRIs show efficacy in the usual antidepressant ranges of dosing (see Table 13.1). The high-potency benzodiazepines alprazolam and clonazepam are also useful in SAD. However, monotherapy with benzodiazepines on a PRN basis is not advised unless the anxiety is related to only a very circumscribed set of circumstances, and potential cognitive dulling or mild-to-moderate impairment of motor coordination caused by the medication would not interfere with the patient's ability to function safely and effectively in the fear-inducing situation. For reasons stated elsewhere in this chapter, clonazepam is generally a preferred agent among the benzodiazepines, and the usual dosing for SAD is 0.5–1 mg daily in two divided doses. For performance-only-type SAD, beta-blockers have shown to be quite helpful. They are thought to suppress the distressing physical symptoms of anxiety caused by excessive sympathetic nervous system activity, such as palpitations, sweating, and tremor. Pregabalin has been found to be effective in doses ranging from 150 to 600 mg daily in two to three divided doses, although the best balance of efficacy and adverse effects has been demonstrated between 300 and 450 mg daily. Some data suggest that pregabalin may be efficacious in SAD at a high daily dose of 600 mg/day [38].

Generalized Anxiety Disorder

GAD is characterized by persistent excessive worries and anxiety about multiple aspects of life, accompanied by several autonomic hyperarousal symptoms such as poor sleep, irritability, concentration difficulties, restlessness, easy fatigability, and muscle tension. GAD is frequently comorbid with MDD, especially in women.

As with PD and SAD, the treatment of choice for GAD is SSRIs/SNRIs. Several of these antidepressants have FDA approval in the USA for treatment of GAD. These include SSRIs paroxetine and escitalopram and SNRIs venlafaxine and duloxetine. As with other anxiety disorders, any of the medications in the same class may have treatment benefits for GAD, and the best treatment for any given patient depends on their clinical response to the medications and whether or not they experience problematic idiosyncratic adverse effects. If there are comorbid psychiatric and nonpsychiatric conditions, then it may be helpful to choose a first-line agent that can address both. For instance, because GAD tends to co-occur with somatic syndromes such as chronic pain and fibromyalgia, it would be reasonable to pursue treatment

with duloxetine first, because this drug has FDA approval for these conditions as well. Considerations for dosing and titration of SSRIs/SNRIs are very similar to those for those for PD.

Although it does not have FDA approval for GAD, the relatively new multimodal "SSRI-plus" antidepressant Vilazodone (*Viibryd*) theoretically should be useful and has preliminary evidence of efficacy for GAD. Vilazodone acts both as an SSRI and as a 5HT-1A partial agonist and thus shares properties of both SSRIs and buspirone. A meta-analysis of three randomized controlled trials of Vilazodone showed efficacy for GAD at doses between 20 and 40 mg daily, albeit with a small effect size and nontrivial dropout due to adverse effects [58]. To date, there is insufficient data to establish Vilazodone as a first-line treatment for GAD.

Pregabalin is approved for treatment of GAD in Europe but does not carry FDA approval for this indication in the USA to date. Dosing is similar to that employed for SAD, as discussed in the previous section. Post hoc analysis of several trials also supports efficacy for treating depressive symptoms associated with GAD using pregabalin [52].

In appropriate patients, usually those who have had inadequate responses or intolerable adverse effects to multiple trials of SSRIs/SNRIs and buspirone, maintenance benzodiazepines remain useful as either monotherapy or adjunctive treatment for GAD. There is no evidence for differential efficacy between the various benzodiazepines for GAD, but generally maintenance treatment with longer half-life agents such as clonazepam and diazepam is preferable because these are associated with less pill-taking and reduced risk of inter-dose anxiety. The principles discussed regarding benzodiazepine prescribing in previous sections apply to GAD as well, namely, avoiding prescribing in those with active or recent substance use problems and starting low and titrating to the lowest dose needed for acceptable symptom management.

Conclusions and Future Directions

While a variety of agents are effective for the treatment of anxiety disorders, SSRIs and SNRIs are the consensus first-line medications given their efficacy and tolerability. Although benzodiazepines are effective, rapidly acting, and relatively well tolerated, their lack of efficacy for comorbid depression and concerns about risk of abuse and dependence limits their use. Antipsychotic, anticonvulsant, and adrenergic antagonist agents may play a role in the pharmacological management of anxiety disorders but should not be considered as first-line strategies. Despite the number of treatments available, many patients with anxiety disorders only partially respond despite extensive trials and combinations of medications. Thus, drugs with novel mechanisms of action targeting various brain receptors and neuronal circuits are currently under investigation. A number of studies have examined the efficacy of oxytocin, a neuropeptide involved in affiliation behaviors, to decrease anxiety, with inconclusive data [11]. Finally, recent advances in the understanding of the role of

the endocannabinoid system in emotion regulation have paved the way to preclinical and clinical studies currently underway examining the therapeutic effects of inhibiting fatty acid amide hydrolase (FAAH), an enzyme involved in deactivating this pathway [29]. Clearly, more research examining the role of these stress pathways and neurotransmitter systems is warranted.

References

1. Abelson JL, Glitz D, Cameron OG, Lee MA, Bronzo M, Curtis GC. Blunted growth hormone response to clonidine in patients with generalized anxiety disorder. Arch Gen Psychiatry. 1991;48(2):157–62.
2. American Psychiatric Association. Practice guideline for the treatment of patients with panic disorder. Washington, DC, USA: American Psychiatric Association; 2009.
3. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord. 2000;58(1):19–36.
4. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. Dialogues Clin Neurosci. 2017;19(2):93–107.
5. Bandelow B, Sher L, Bunevicius R, Hollander E, Kasper S, Zohar J, Moller HJ, WFSBP Task Force on Mental Disorders in Primary Care, WFSBP Task Force on Anxiety Disorders, OCD and PTSD. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Pract. 2012;16(2):77–84.
6. Boschen MJ. A meta-analysis of the efficacy of pregabalin in the treatment of generalized anxiety disorder. Can J Psychiatr. 2011;56(9):558–66.
7. Bruce SE, Vasile RG, Goisman RM, Salzman C, Spencer M, Machan JT, Keller MB. Are benzodiazepines still the medication of choice for patients with panic disorder with or without agoraphobia? Am J Psychiatry. 2003;160(8):1432–8.
8. Canadian Psychiatric Association. Clinical practice guidelines. Management of anxiety disorders. Can J Psychiatr. 2006;51(8 Suppl 2):9S–91S.
9. Canton J, Scott KM, Glue P. Optimal treatment of social phobia: systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2012;8:203–15.
10. Coplan JD, Lydiard RB. Brain circuits in panic disorder. Biol Psychiatry. 1998;44(12):1264–76.
11. De Cagna F, Fusar-Poli L, Damiani S, Rocchetti M, Giovanna G, Mori A, Politi P, Brondino N. The role of intranasal oxytocin in anxiety and depressive disorders: a systematic review of randomized controlled trials. Clin Psychopharmacol Neurosci. 2019;17(1):1–11.
12. Den Boer JA, Westenberg HG. Effect of a serotonin and noradrenaline uptake inhibitor in panic disorder; a double-blind comparative study with fluvoxamine and maprotiline. Int Clin Psychopharmacol. 1988;3(1):59–74.
13. Ernst M, Lago T, Davis A, Grillon C. The effects of methylphenidate and propranolol on the interplay between induced-anxiety and working memory. Psychopharmacology. 2016;233(19–20):3565–74.
14. Fava M, Rankin M. Sexual functioning and SSRIs. J Clin Psychiatry. 2002;63(Suppl 5):13–6; discussion 23–15
15. Federico A, Tamburin S, Maier A, Faccini M, Casari R, Morbioli L, Lugoboni F. Multifocal cognitive dysfunction in high-dose benzodiazepine users: a cross-sectional study. Neurol Sci. 2017;38(1):137–42.
16. Gao K, Ganocy SJ, Conroy C, Brownrigg B, Serrano MB, Calabrese JR. A placebo controlled study of quetiapine-XR in bipolar depression accompanied by generalized anxiety with and without a recent history of alcohol and cannabis use. Psychopharmacology. 2017;234(15):2233–44.

17. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry. 2006;163(11):1898–904.
18. Goddard AW, Brouette T, Almai A, Jetty P, Woods SW, Charney D. Early coadministration of clonazepam with sertraline for panic disorder. Arch Gen Psychiatry. 2001;58(7):681–6.
19. Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. Am J Psychiatry. 2000;157(4):493–505.
20. Hayes PE, Schulz SC. Beta-blockers in anxiety disorders. J Affect Disord. 1987;13(2):119–30.
21. Herman JB, Rosenbaum JF, Brotman AW. The alprazolam to clonazepam switch for the treatment of panic disorder. J Clin Psychopharmacol. 1987;7(3):175–8.
22. Iny LJ, Pecknold J, Suranyi-Cadotte BE, Bernier B, Luthe L, Nair NP, Meaney MJ. Studies of a neurochemical link between depression, anxiety, and stress from [3H]imipramine and [3H] paroxetine binding on human platelets. Biol Psychiatry. 1994;36(5):281–91.
23. Kalus O, Asnis GM, Rubinson E, Kahn R, Friedman JM, Iqbal N, Grosz D, van Praag H, Cahn W. Desipramine treatment in panic disorder. J Affect Disord. 1991;21(4):239–44.
24. Katzman MA, Brawman-Mintzer O, Reyes EB, Olausson B, Liu S, Eriksson H. Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. Int Clin Psychopharmacol. 2011;26(1):11–24.
25. Kennedy SH, Rizvi S. Sexual dysfunction, depression, and the impact of antidepressants. J Clin Psychopharmacol. 2009;29(2):157–64.
26. Lee KU, Lee YM, Nam JM, Lee HK, Kweon YS, Lee CT, Jun TY. Antidepressant-induced sexual dysfunction among newer antidepressants in a naturalistic setting. Psychiatry Investig. 2010;7(1):55–9.
27. Louie AK, Lewis TB, Lannon RA. Use of low-dose fluoxetine in major depression and panic disorder. J Clin Psychiatry. 1993;54(11):435–8.
28. MacGillivray S, Arroll B, Hatcher S, Ogston S, Reid I, Sullivan F, Williams B, Crombie I. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. BMJ. 2003;326(7397):1014.
29. Marco EM, Rapino C, Caprioli A, Borsini F, Laviola G, Maccarrone M. Potential therapeutic value of a novel FAAH inhibitor for the treatment of anxiety. PLoS One. 2015;10(9):e0137034.
30. McNally RJ. Anxiety sensitivity and panic disorder. Biol Psychiatry. 2002;52(10):938–46.
31. Mezhebovsky I, Magi K, She F, Datto C, Eriksson H. Double-blind, randomized study of extended release quetiapine fumarate (quetiapine XR) monotherapy in older patients with generalized anxiety disorder. Int J Geriatr Psychiatry. 2013;28(6):615–25.
32. Modigh K, Westberg P, Eriksson E. Superiority of clomipramine over imipramine in the treatment of panic disorder: a placebo-controlled trial. J Clin Psychopharmacol. 1992;12(4):251–61.
33. Moroz G, Rosenbaum JF. Efficacy, safety, and gradual discontinuation of clonazepam in panic disorder: a placebo-controlled, multicenter study using optimized dosages. J Clin Psychiatry. 1999;60(9):604–12.
34. Nutt DJ. Antidepressants in panic disorder: clinical and preclinical mechanisms. J Clin Psychiatry. 1998;59(Suppl 8):24–8; discussion 29
35. Otto MW, McHugh RK, Kantak KM. Combined pharmacotherapy and cognitive-behavioral therapy for anxiety disorders: medication effects, glucocorticoids, and attenuated treatment outcomes. Clin Psychol (New York). 2010;17(2):91–103.
36. Otto MW, Pollack MH, Sabatino SA. Maintenance of remission following cognitive behavior therapy for panic disorder: possible deleterious effects of concurrent medication treatment. Behav Ther. 1996;27(3):473.
37. Pande AC, Davidson JR, Jefferson JW, Janney CA, Katzelnick DJ, Weisler RH, Greist JH, Sutherland SM. Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol. 1999;19(4):341–8.
38. Pande AC, Feltner DE, Jefferson JW, Davidson JR, Pollack M, Stein MB, Lydiard RB, Futterer R, Robinson P, Slomkowski M, DuBoff E, Phelps M, Janney CA, Werth JL. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. J Clin Psychopharmacol. 2004;24(2):141–9.

39. Perna G, Alciati A, Riva A, Micieli W, Caldirola D. Long-term pharmacological treatments of anxiety disorders: an updated systematic review. Curr Psychiatry Rep. 2016;18(3):23.
40. Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, Otto MW. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. J Psychopharmacol. 2003;17(3):276–82.
41. Primeau F, Fontaine R. GABAergic agents and panic disorder. Biol Psychiatry. 1988;24(8):942–3.
42. Redmond DE Jr, Huang YH. Current concepts. II. New evidence for a locus coeruleus-norepinephrine connection with anxiety. Life Sci. 1979;25(26):2149–62.
43. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety. 2000;12(Suppl 1):2–19.
44. Rosenberg KP, Bleiberg KL, Koscis J, Gross C. A survey of sexual side effects among severely mentally ill patients taking psychotropic medications: impact on compliance. J Sex Marital Ther. 2003;29(4):289–96.
45. Sasson Y, Iancu I, Fux M, Taub M, Dannon PN, Zohar J. A double-blind crossover comparison of clomipramine and desipramine in the treatment of panic disorder. Eur Neuropsychopharmacol. 1999;9(3):191–6.
46. Seedat S, Stein MB. Double-blind, placebo-controlled assessment of combined clonazepam with paroxetine compared with paroxetine monotherapy for generalized social anxiety disorder. J Clin Psychiatry. 2004;65(2):244–8.
47. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology. 2010;35(1):169–91.
48. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. Am J Psychiatry. 2006;163(1):41–7.
49. Simon NM, Kaufman RE, Hoge EA, Worthington JJ, Herlands NN, Owens ME, Pollack MH. Open-label support for duloxetine for the treatment of panic disorder. CNS Neurosci Ther. 2009;15(1):19–23.
50. Sinclair LI, Christmas DM, Hood SD, Potokar JP, Robertson A, Isaac A, Srivastava S, Nutt DJ, Davies SJ. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. Br J Psychiatry. 2009;194(6):483–90.
51. Soyka M. Treatment of benzodiazepine dependence. N Engl J Med. 2017;376(24):2399–400.
52. Stein DJ, Baldwin DS, Baldinetti F, Mandel F. Efficacy of pregabalin in depressive symptoms associated with generalized anxiety disorder: a pooled analysis of 6 studies. Eur Neuropsychopharmacol. 2008;18(6):422–30.
53. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, Rochester G. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ. 2009;339:b2880.
54. Suttajit S, Srisurapanont M, Maneeton N, Maneeton B. Quetiapine for acute bipolar depression: a systematic review and meta-analysis. Drug Des Devel Ther. 2014;8:827–38.
55. Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database Syst Rev. 2013;5:CD003382.
56. Uzun S, Kozumplik O, Jakovljevic M, Sedic B. Side effects of treatment with benzodiazepines. Psychiatr Danub. 2010;22(1):90–3.
57. Yamada M, Yasuhara H. Clinical pharmacology of MAO inhibitors: safety and future. Neurotoxicology. 2004;25(1–2):215–21.
58. Zareifopoulos N, Dylja I. Efficacy and tolerability of vilazodone for the acute treatment of generalized anxiety disorder: a meta-analysis. Asian J Psychiatr. 2017;26:115–22.
59. Zwanzger P, Rupprecht R. Selective GABAergic treatment for panic? Investigations in experimental panic induction and panic disorder. J Psychiatry Neurosci. 2005;30(3):167–75.

Chapter 14
Mind–Body Treatments for Anxiety Disorders

Marco Maiello, Meredith J. Ward, and Eric Bui

Introduction

Anxiety disorders are among the most prevalent psychiatric disorders in the United States with a prevalence of 20% in the general population [60, 61]. Anxiety disorders, including panic disorder (PD), social anxiety disorder (SAD), and generalized anxiety disorder (GAD), are often comorbid with other psychiatric disorders (see Chap. 5) such as depression, substance use disorder, and bipolar disorder [15, 62, 69, 74, 80] and cause significant distress and impairment. Currently, their first-line treatments include pharmacological approaches, specifically antidepressant medications, as well as cognitive behavioral therapy [70].

Selective serotonin reuptake inhibitor antidepressants do not meet the needs of every individual seeking anxiety treatment, with many individuals dissatisfied by side effects [84]. For those who agree to try the medications, response rates are only around 60% [8], with many patients experiencing little, if any decrease, of symptoms. To maintain initial effects, if an individual does respond to psychopharmacological treatment, long-term treatment is usually necessary [6]. Yet, many patients

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find remaining on antidepressant medication permanently an unappealing option [98], while others never adhere to taking the daily medications to begin with [83, 89].

Cognitive behavioral therapy (CBT) is an evidence-based psychological intervention recommended as the non-pharmaceutical first-line treatment for anxiety disorders (see Chap. 12); however, its reach is limited by the lack of availability of trained therapists in the community [49]. Recent efforts to improve access to evidence-based therapies include the development of telemedicine and other remote delivery methods through a digital platform (see Chap. 16); however, those efforts are still limited by the availability of trained therapists (see Chap. 18).

In the past couple of decades, the scientific interest in alternative medicine approaches has increased, reflecting patients' interest. Among those, mind–body approaches and mindfulness-based approaches have received the most attention [59]. Mindfulness-based approaches are thought to target the physiological stress response by teaching practical skills to help regulate the arousal associated with the stress response [21, 37, 45]. It is posited that long-term practice of these skills can help improve adaptive emotion regulation and thus decrease negative emotions, like stress. Under normal circumstances, exposure to a threat (i.e., stressor) activates a series of physiological responses by preparing the body to cope with the danger, increasing the metabolism, and increasing the heart rate and blood pressure (i.e., normal stress response). An exaggerated activation of this stress response either in intensity or in duration is thought to underlie the pathophysiology of anxiety disorders [20, 27, 32, 34, 54, 96].

Most mind–body approaches teach, to a certain degree, how to be "mindful," that is, to remain focused on present thoughts and emotions including during stressful experiences, thus increasing the ability to cope with stressors. Mindfulness appears to increase decentering (i.e., detachment [9, 21, 44, 97]), which may in turn help with decreasing negative cognitions. The effect of decreasing emotional reactivity has been observed in neuroimaging studies, which show decreased activation in emotional amygdala response in response to provocative stimuli [48] modulating the emotional component of arousal [75].

Mind–Body Interventions

Mindfulness-Based Interventions

Mindfulness training, historically, originates from Buddhist philosophy and practice [66, 85]. In mindfulness-based practices, focusing on the act of perceiving can help apprehend subjectivity of their experiences. Mindfulness practices thus aim to increase awareness that thoughts are distinct from the reality [93], creating an opportunity to rethink negative thoughts and accept unpleasant emotions with the understanding that they will pass [10]. Mindfulness meditation practices include a variety of exercises including the body scan, in which the subject learns to pay attention to each part of their body and the sensations arising from it; sitting meditation, in which the subject focuses on their respiration and the emergence of their

thoughts; or walking meditation, where the subject focuses on sensations from their feet and legs during the act of walking [1, 4, 22, 50, 76]. In the past couple decades, mindfulness training has been manualized into protocols created for use in contemporary settings, such as mindfulness-based stress reduction and mindfulness-based cognitive therapy.

Mindfulness-Based Stress Reduction (MBSR)

MBSR is a mindfulness-based approach that has been developed to manualize Buddhist meditation practices for the contemporary psychiatric setting [55]. The standard class consists of eight 2.5-hour weekly classes delivered in a group setting, and 1 day-long class around the sixth week. In order to be certified, the instructors of the course go through a practice-based training to ensure adequate understanding of the core philosophies and experience administering the training modules. The instructors ask participants to meditate daily at home, for around 45 minutes. In addition to these practices, MBSR also includes some *Hatha* yoga exercises (see Yoga section for details) designed to reinforce the connection between the body and bodily sensations and the connection between them and emotional experience. Ultimately, the hope is that subjects leave the class with a newfound ability to let experience unfold in front of them without preconceptions, personalization, and maladaptive reaction. The overarching goal is to teach acceptance of the present moment, and for patients to allow their thoughts to come and go freely, without holding on to them [55]. This retraining of judgment and skill training of the relaxation response aim to help reduce anxiety symptom severity.

Mindfulness-Based Cognitive Therapy (MBCT)

MBCT was originally developed as a relapse prevention tool in subjects who had recovered from a depressive episode and is a program that blends the meditation principles of MBSR with those of cognitive therapy [85]. MBCT adds mindfulness-based elements to traditional CBT to teach detection of worsening mood and address relapse of ruminative thoughts which are related to the recurrences of mood episodes and anxiety [85]. Building upon the MBSR protocol, MBCT comprises an 8-week program of weekly sessions lasting 2.5 hours with daily exercises and a 1-day-long class. Both MBSR and MBCT include similar mindfulness training exercises; however, MBCT explicitly addresses negative and ruminative thinking.

The Stress Management and Resiliency Training – Relaxation Response Resiliency Program (SMART-3RP)

Mind–body group programs to promote adaptation to stress and enhance resiliency have been offered at the *Benson-Henry Institute for Mind Body Medicine* for the past couple decades and have been recently formalized into the SMART-3RP [77].

This program integrates Benson's theory of the relaxation response, with elements of positive psychology and cognitive therapy [77]. The relaxation response is conceptualized as the counterpart of the stress response and can be triggered by a series of techniques such as mindfulness meditation or *Hatha* yoga so as to dampen the sympathetic hyperarousal associated with the stress response [28]. The main components of the SMART-3RP include techniques to induce the relaxation response, the creation of adaptive perspective in response to stressful situations, and elements of self-compassion [77]. While the mechanism of action of the SMART-3RP on mental health is thought to be the relaxation response, mindfulness training is a central component essential to achieving such relaxation response. The program consists of eight sessions with one weekly class lasting 1.5 hours [77]. The SMART-3RP introduces lifestyle behaviors that promote the relaxation response, increasing the ability to build social support, develop adaptive thinking to counter stress-activating thoughts, cultivate optimism and positive thinking, and promote a sense of spiritual connectedness with others [77]. The SMART-3RP has been recently adapted to meet the specific needs of veterans [92], military caregivers [16], and grievers [17].

Evidence Base

Several meta-analyses attempted to examine the efficacy of mindfulness-based interventions on anxiety with effect sizes ranging from small to large [36, 43, 63, 90, 100]. For example, based on 39 studies totaling 1140 participants receiving mindfulness-based therapy for a variety of medical conditions, Hofmann et al. [43] found Hedges' g of 0.63 for mindfulness-based therapy for anxiety. Among patients with anxiety and mood disorders, the intervention was associated with effect sizes of $g = 0.97$ and 0.95 regarding anxiety and mood symptom improvement, generally. Another meta-analysis [100] found an effect of $g = 1.08$ for mindfulness- and acceptance-based interventions on anxiety symptoms based on 19 trials including $n = 491$ patients. Of these trials, 5 were randomized controlled trials (RCT)s and 14 were uncontrolled trials. There is significant support for the efficacy of mindfulness- and acceptance-based approaches for improving anxiety symptoms among patients with anxiety and mood disorder. Considering the continued interest from the community, patient-centered research should continue to test the effectiveness of these approaches compared to current gold standard treatments for anxiety, like antidepressant medication and CBT.

Movement-Based Interventions

Movement-based approaches also build on Buddhist philosophy, yet they use physical movement to a higher degree than mindfulness training programs such as MBSR. They comprise a variety of ancient practices (e.g., yoga, tai chi) that are

based on the association of meditation, breathing techniques, and posture. Their benefits on mental and physical well-being have later been suggested to result from positive effects on the immune [31, 39], endocrine [57, 103], and neurovegetative systems [110].

Yoga

Yoga is an ancient discipline that was developed as a process for spiritual growth. Research has confirmed its beneficial effects may be applied to the treatment of some physical and psychological conditions ailments [5]. Yoga traditions promote the sequence of specific postures (*asanas*) while reminding subjects to breathe, sometimes completing specific breathing exercises (pranayama [52]). The most studied subtype of yoga is *Hatha* yoga, which is the type of yoga we commonly refer to when talking about yoga, and whose main focus is posture [14]. *Hatha* yoga itself constitutes a category that embraces other popular yoga practices that include *Iyengar* yoga (postural alignment or asanas), *Vinyasa* yoga (posture and breathing association), *Sudarshan Kriya* yoga (SKY; mainly breathing [*pranayama*]), *Bikram* yoga (more demanding postural and breathing exercises), *Kripalu* yoga (awareness of self, emotions and cognition), and *Ashtanga* yoga (sequenced postures and breathing exercises; [71, 95]).

Yoga was proposed as a potential treatment for anxiety disorders as it has been shown to reduce stress [88] and improve neuroplasticity [108]. Also, it has been shown that specific postures are associated with improved emotion regulation [99] and increased positive affects [106] suggesting the possibility to use different postures routinely to regulate mood. Yoga also appears to have a positive effect on the inflammatory system [31], endocrine system [57], and the parasympathetic nervous systems [110]. In addition, preliminary results on the use of yoga in several medical conditions (i.e., cancer, diabetes, chronic low back pain) are promising, as far as reducing symptoms and improving quality of life, but need further definitive confirmation [7]. Among other supporting evidence, yoga has been shown to exert an effect on neurotransmitters involved in the physiological stress response [51, 91]. A recent meta-analysis across 17 studies (pooled $N = 501$) found a pre- to post-*Hatha* yoga intervention Hedges' g of 0.44 and a controlled (between groups) Hedges' g of 0.61 on anxiety symptom severity [41], and another including eight RCTs (pooled $N = 319$) reported large effects compared to active comparators (standard mean differences $= -0.86$) [24].

Tai Chi

Another movement-based approach, tai chi, originated in China as a type of mindfulness-based exercise and has been used as a form of therapy for multiple illnesses since the twelfth century [40]. Tai chi utilizes slow, graceful movements where practitioners shift their weight between the feet while moving their arms.

This practice comprises elements that combine meditation, martial arts, guided imagery, and deep breathing. Tai chi has been suggested to be beneficial for cognitive abilities like memory and concentration; some chronic illnesses including cancer, arthritis, and high blood pressure; as well as psychiatric conditions like depression and anxiety [105, 109]. Since tai chi is a low-cost intervention that may be implemented without many auxiliary materials many Western countries are approaching this practice and considering it as an alternative and/or complementary treatment for illnesses, including anxiety disorders [104].

Massage Therapy

Massage therapy is considered by the National Center for Complementary and Integrative Health as a "body" technique, a type of mind–body intervention that encompasses external manipulation of the body [68]. Although several varieties of massage therapy exist, they all incorporate massaging tissue. Massage has been proposed as a potential treatment for anxiety disorders given its effects on muscle tension [12, 19].

Evidence Base for Specific Anxiety Disorders

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive worries, nervousness, fatigability, concentration problems, agitation, somatic symptoms, and sleep disruption ongoing for at least 6 months. Often the content of the excessive worry centers around everyday matters such as, health, relationships, work, and general future planning [2].

As individuals with GAD have been found to have lower levels of self-reported mindfulness compared to healthy subjects [46], MBSR has been proposed as a treatment for GAD [56]. In a small RCT ($N = 33$), MBSR was associated with greater decreases in symptoms of anxiety, worry, and depression compared to a non-specified control condition [3]. Another RCT comparing MBSR to a stress education control group [46] reported that MBSR was associated with a significantly greater reduction in anxiety symptoms measured by the Clinical Global Impression of Severity and Improvements and the Beck Anxiety Inventory and greater reductions in anxiety and distress ratings in response to the Trier Social Stress Test, although the differences were not significant on the anxiety symptom severity measured by the HAM-A. Secondary analyses of this RCT suggest that the decrease in GAD symptoms may be mediated by increases in decentering, providing support for mindfulness training as the "active ingredient" of MBSR [44]. Other studies also suggest that MBSR may affect several brain mechanisms that are dysregulated in GAD [38, 72, 73, 78, 102]. For example, individuals with GAD, compared to

healthy subjects, exhibit a weaker connectivity between the prefrontal cortex and the amygdala [29, 67] that improve after MBSR through changes in fronto-limbic areas [47].

Some data on the efficacy of MBCT for the treatment of GAD are available. Two small open pilot studies showed a decrease in anxiety symptom severity from pre- to post-MBCT [23, 30], suggesting that MBCT may be efficacious for the treatment of GAD. A recent RCT among *N* = 182 adults with GAD treatment as usual found that both MBCT- and CBT-based group psychoeducation were associated with lower GAD symptom severity at the end of treatment (2 months) and 5-month follow-up compared to treatment as usual [107]. The study failed to show an efficacy of MBCT compared to CBT-based group psychoeducation.

Several studies have focused on the use of yoga for GAD. Two small open-label studies provide some preliminary effectiveness data for *Sudarshan Kriya yoga* (SKY) in GAD [25, 58]. Similar results on *Kundalini* yoga were found in a more recent small RCT [33] that reported that 8 weeks of *Kundalini* yoga resulted in lower levels of anxiety compared to treatment as usual among women with GAD. However, another study among *N* = 40 individuals with GAD failed to show a difference between *Hatha* yoga group and a control condition [81]. Despite emerging data, large randomized trials are needed to definitively confirm the efficacy of yoga for GAD. A large RCT examining the efficacy of yoga compared to CBT and an attention control condition is being currently completed [42]. The results of this trial will provide the needed evidence base to recommend yoga as a first-line treatment for GAD.

As far as the use of massage therapy for the treatment of GAD, an RCT comparing therapeutic massage vs. thermotherapy vs. relaxing room therapy among *N* = 68 individuals with GAD failed to find a significant difference across groups, although participants significantly improved from pre- to posttreatment within each condition [87]. A recent small RCT found that Swedish massage therapy applied twice weekly over 6 weeks was more efficacious than a "light touch" control condition in decreasing GAD symptom severity and biomarkers of stress including heart rate and cortisol levels [82].

Social Anxiety Disorder

Individuals who suffer from social anxiety disorder (SAD) fear being judged negatively in social contexts, producing a burden in their daily living and occupations [26]. Individuals with SAD tend to focus on the way others' view them, sometimes avoiding situations where their performance would be judged (e.g., giving a speech, participating in class, meeting new people at parties). Mindfulness training might help reduce the self-oriented thoughts in patients with SAD, reduce their negative self-evaluation, and diminish the preoccupation with the evaluation of others [94]. A small study failed to show efficacy of MBSR versus aerobic exercise for individuals with SAD, although both groups improved compared to a no-treatment compari-

son group [53]. In addition, two other trials comparing MBSR to group cognitive behavioral therapy (CBT) found that both MBSR and CBT were effective on a range of outcomes including anxiety symptom severity, negative self-oriented thoughts, self-esteem, and quality of life [35, 65].

An open-label trial reported symptom reduction in an individual receiving a course of MBCT [11]; however, a randomized trial failed to show a significant difference between MBCT and group CBT [79]. Due to the paucity of results and scarce evidence, it will be necessary to conduct larger RCT to further assess the efficacy of MBCT in social anxiety and recommend it as a potential first-line treatment.

Panic Disorder

Panic disorder (PD) is a condition characterized by repeated panic attacks within a 1-month period. Patients affected by this condition are persistently worried about the next attack and its consequences. A panic attack may or may not be triggered by a specific cause and is characterized by the abrupt presentation of distressing physical and cognitive symptoms of anxiety (such as heart palpitations, trouble breathing, dizziness, feeling detached from oneself, worrying about the next panic attack). This condition may also be accompanied by agoraphobia, which is the avoidance of specific situations or places where one feels unsafe in the event of a panic attack [2].

Only few studies exist regarding the usefulness of mind–body treatments for PD. Results from an open trial among $N = 31$ patients with PD receiving pharmacotherapy indicated a decrease in PD symptom severity from pre- to post-MBCT [64]. Results from another small study ($N = 20$ with PD) also revealed that adjunctive yoga was associated with greater symptom reduction compared to CBT only [101].

Recommendations and Future Directions

While the practice of mindfulness has its roots in ancient Eastern culture, its use has been incorporated into Western medicine. Mounting evidence supports the efficacy of mind–body interventions, particularly MBSR and MBCT for anxiety disorders. The available evidence base regarding the efficacy of mindfulness-based and mind–body interventions for anxiety disorders varies across anxiety disorders and across interventions.

Despite recent advances, more research is clearly necessary to confirm the emerging efficacy data. More importantly, comparative effectiveness data are needed to identify the role of mind–body interventions with regard to existing evidence-based treatment approaches such as CBT or pharmacotherapy [86]. For example, it is unclear at this point whether mind body programs such as MBSR or MBCT should be proposed as an adjunct treatment, or as a first-line treatment, and, if the latter, to which patients. A multisite comparative effectiveness randomized trial of MBSR vs.

the selective serotonin reuptake inhibitor antidepressant escitalopram across all anxiety disorders is currently underway (NCT03522844) and should bring some answers. Further, as mind–body approaches target the stress pathway, they may also be efficacious on other conditions which pathophysiology involves the stress response, including posttraumatic stress disorder [13] and complicated grief [18].

In conclusion, there is growing interest in mind–body interventions for the treatment of anxiety disorders. The approaches reviewed in this chapter may be beneficial for those patients who need mental health support but are reluctant to take medications and have limited access to evidence-based psychotherapy.

References

1. Adele MH, Feldman G. Clarifying the construct of mindfulness in the context of emotion regulation and the process of change in therapy. Clin Psychol Sci Pract. 2004;11(3):255–62.
2. APA. Diagnostic and statistical manual of mental disorders: DSM-5TM. 5th ed. Arlington: American Psychiatric Publishing; 2013.
3. Asmaee Majid S, Seghatoleslam T, Homan H, Akhvast A, Habil H. Effect of mindfulness based stress management on reduction of generalized anxiety disorder. Iran J Public Health. 2012;41(10):24–8.
4. Baer RA. Mindfulness training as a clinical intervention: a conceptual and empirical review. Clin Psychol Sci Pract. 2003;10(2):125–43.
5. Balasubramaniam M, Telles S, Doraiswamy PM. Yoga on our minds: a systematic review of yoga for neuropsychiatric disorders. Front Psych. 2012;3:117.
6. Baldwin DS, Waldman S, Allgulander C. Evidence-based pharmacological treatment of generalized anxiety disorder. Int J Neuropsychopharmacol. 2011;14(5):697–710.
7. Bayley-Veloso R, Salmon PG. Yoga in clinical practice. Mindfulness. 2016;7(2):308.
8. Berger W, Mendlowicz MV, Marques-Portella C, Kinrys G, Fontenelle LF, Marmar CR, Figueira I. Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review. Prog Neuro-Psychopharmacol Biol Psychiatry. 2009;33(2):169–80.
9. Bieling PJ, Hawley LL, Bloch RT, Corcoran KM, Levitan RD, Young LT, MacQueen GM, Segal ZV. Treatment-specific changes in decentering following mindfulness-based cognitive therapy versus antidepressant medication or placebo for prevention of depressive relapse. J Consult Clin Psychol. 2012;80(3):365–72.
10. Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, Segal ZV, Abbey S, Speca M, Velting D, Devins G. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract. 2004;11(3):230–41.
11. Bogels SM, Sijbers GFVM, Voncken M. Mindfulness and task concentration training for social phobia: a pilot study. J Cogn Psychother. 2006;20(1):33.
12. Boitor M, Martorella G, Maheu C, Laizner AM, Gelinas C. Effects of massage in reducing the pain and anxiety of the cardiac surgery critically ill-a randomized controlled trial. Pain Med. 2018;19(12):2556–69.
13. Boyd JE, Lanius RA, McKinnon MC. Mindfulness-based treatments for posttraumatic stress disorder: a review of the treatment literature and neurobiological evidence. J Psychiatry Neurosci. 2018;43(1):7–25.
14. Bridges L, Sharma M. The efficacy of yoga as a form of treatment for depression. J Evid Based Complementary Altern Med. 2017;22(4):1017–28.
15. Buckner JD, Schmidt NB, Lang AR, Small JW, Schlauch RC, Lewinsohn PM. Specificity of social anxiety disorder as a risk factor for alcohol and cannabis dependence. J Psychiatr Res. 2008;42(3):230–9.

16. Bui E, Blackburn AM, Brenner LH, Laifer LM, Park ER, Fricchione GL, Sylvia LG. Military and veteran caregivers' perspectives of stressors and a mind-body program. Issues Ment Health Nurs. 2018a;39(10):850–7.

17. Bui E, Chad-Friedman E, Wieman S, Grasfield RH, Rolfe A, Dong M, Park ER, Denninger JW. Patient and provider perspectives on a mind-body program for grieving older adults. Am J Hosp Palliat Care. 2018b;35(6):858–65.

18. Bui E, Okereke O. From bereavement to grief to cognitive decline: a call for novel treatment and prevention approaches. Am J Geriatr Psychiatry. 2018;26(4):461–2.

19. Buttagat V, Eungpinichpong W, Chatchawan U, Arayawichanon P. Therapeutic effects of traditional Thai massage on pain, muscle tension and anxiety in patients with scapulocostal syndrome: a randomized single-blinded pilot study. J Bodyw Mov Ther. 2012;16(1):57–63.

20. Bystritsky A, Maidenberg E, Craske MG, Vapnik T, Shapiro D. Laboratory psychophysiological assessment and imagery exposure in panic disorder patients. Depress Anxiety. 2000;12(2):102–8.

21. Carmody J, Baer RA, Lykins ELB, Olendzki N. An empirical study of the mechanisms of mindfulness in a mindfulness-based stress reduction program. J Clin Psychol. 2009;65(6):613–26.

22. Chiesa A, Serretti A. A systematic review of neurobiological and clinical features of mindfulness meditations. Psychol Med. 2010;40(8):1239.

23. Craigie MA, Rees CS, Marsh A, Nathan P. Mindfulness-based cognitive therapy for generalized anxiety disorder: a preliminary evaluation. Behavioural and Cognitive Psychotherapy. 2008;36(5):553.

24. Cramer H, Lauche R, Anheyer D, Pilkington K, de Manincor M, Dobos G, Ward L. Yoga for anxiety: a systematic review and meta-analysis of randomized controlled trials. Depress Anxiety. 2018;35(9):830–43.

25. Doria S, de Vuono A, Sanlorenzo R, Irtelli F, Mencacci C. Anti-anxiety efficacy of Sudarshan Kriya yoga in general anxiety disorder: a multicomponent, yoga based, breath intervention program for patients suffering from generalized anxiety disorder with or without comorbidities. J Affect Disord. 2015;184:310–7.

26. DSM-5. Diagnostic and statistical manual of mental disorders: DSM-5TM. 5th ed. Arlington: American Psychiatric Publishing; 2013.

27. Duncko R, Makatsori A, Fickova E, Selko D, Jezova D. Altered coordination of the neuroendocrine response during psychosocial stress in subjects with high trait anxiety. Prog Neuro-Psychopharmacol Biol Psychiatry. 2006;30(6):1058–66.

28. Dusek JA, Benson H. Mind-body medicine: a model of the comparative clinical impact of the acute stress and relaxation responses. Minn Med. 2009;92(5):47–50.

29. Etkin A, Prater KE, Schatzberg AF, Menon V, Greicius MD. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry. 2009;66(12):1361–72.

30. Evans S, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. J Anxiety Disord. 2008;22(4):716–21.

31. Falkenberg RI, Eising C, Peters ML. Yoga and immune system functioning: a systematic review of randomized controlled trials. J Behav Med. 2018;41(4):467.

32. Fisher AJ, Newman MG. Heart rate and autonomic response to stress after experimental induction of worry versus relaxation in healthy, high-worry, and generalized anxiety disorder individuals. Biol Psychol. 2013;93(1):65–74.

33. Gabriel MG, Curtiss J, Hofmann SG, Khalsa SBS. Kundalini yoga for generalized anxiety disorder: an exploration of treatment efficacy and possible mechanisms. Int J Yoga Therap. 2018;28(1):97–105.

34. Garcia-Leal C, Parente AC, Del-Ben CM, Guimaraes FS, Moreira AC, Elias LL, Graeff FG. Anxiety and salivary cortisol in symptomatic and nonsymptomatic panic patients and healthy volunteers performing simulated public speaking. Psychiatry Res. 2005;133(2–3):239–52.

35. Goldin PR, Morrison A, Jazaieri H, Brozovich F, Heimberg R, Gross JJ. Group CBT versus MBSR for social anxiety disorder: a randomized controlled trial. J Consult Clin Psychol. 2016;84(5):427–37.
36. Goyal M, Singh S, Sibinga EM, Gould NF, Rowland-Seymour A, Sharma R, Berger Z, Sleicher D, Maron DD, Shihab HM, Ranasinghe PD, Linn S, Saha S, Bass EB, Haythornthwaite JA. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med. 2014;174(3):357–68.
37. Gu J, Strauss C, Bond R, Cavanagh K. How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. Clin Psychol Rev. 2015;37:1–12.
38. Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. Biol Psychiatry. 2003;53(6):494–501.
39. Ho RTH, Wang C-W, Ng S-M, Ho AHY, Ziea ETC, Wong VT, Chan CLW. The effect of T'ai chi exercise on immunity and infections: a systematic review of controlled trials. J Altern Complement Med. 2013;19(5):389.
40. Hoffmann-Smith Kimberly A, Ma A, Yeh C-T, DeGuire Nancy L, Smith Jacqueline P. The effect of tai chi in reducing anxiety in an ambulatory population. J Complement Integr Med. 2009;6(1):14.
41. Hofmann SG, Andreoli G, Carpenter JK, Curtiss J. Effect of hatha yoga on anxiety: a meta-analysis. J Evid Based Med. 2016;9:116.
42. Hofmann SG, Curtiss J, Khalsa SBS, Hoge E, Rosenfield D, Bui E, Keshaviah A, Simon N. Yoga for generalized anxiety disorder: design of a randomized controlled clinical trial. Contemp Clin Trials. 2015;44:70–6.
43. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: a meta-analytic review. J Consult Clin Psychol. 2010;78(2):169–83.
44. Hoge EA, Bui E, Goetter E, Robinaugh DJ, Ojserkis RA, Fresco DM, Simon NM. Change in decentering mediates improvement in anxiety in mindfulness-based stress reduction for generalized anxiety disorder. Cognit Ther Res. 2015;39(2):228–35.
45. Hoge EA, Bui E, Marques L, Metcalf CA, Morris LK, Robinaugh DJ, Worthington JJ, Pollack MH, Simon NM. Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: effects on anxiety and stress reactivity. J Clin Psychiatry. 2013a;74(8):786–92.
46. Hoge EA, Holzel BK, Marques L, Metcalf CA, Brach N, Lazar SW, Simon NM. Mindfulness and self-compassion in generalized anxiety disorder: examining predictors of disability. Evid Based Complement Alternat Med. 2013c;2013:576258.
47. Holzel BK, Hoge EA, Greve DN, Gard T, Creswell JD, Brown KW, Barrett LF, Schwartz C, Vaitl D, Lazar SW. Neural mechanisms of symptom improvements in generalized anxiety disorder following mindfulness training. Neuroimage Clin. 2013;2:448–58.
48. Holzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. Perspect Psychol Sci. 2011;6(6):537–59.
49. HRSA/NCHWA. Substance abuse and mental health services administration/office of policy, planning, and innovation. 2015. National projections of supply and demand for behavioral health practitioners: 2013–2025. Rockville: HRSA; 2015.
50. Ivanovski B, Malhi GS. The psychological and neurophysiological concomitants of mindfulness forms of meditation. Acta Neuropsychiatr. 2007;19(2):76–91.
51. Janakiramaiah N, Gangadhar BN, Naga Venkatesha Murthy PJ, Harish MG, Subbakrishna DK, Vedamurthachar A. Antidepressant efficacy of Sudarshan Kriya yoga (SKY) in melancholia: a randomized comparison with electroconvulsive therapy (ECT) and imipramine. J Affect Disord. 2000;57(1–3):255–9.
52. Javnbakht M, Hejazi Kenari R, Ghasemi M. Effects of yoga on depression and anxiety of women. Complement Ther Clin Pract. 2009;15(2):102–4.
53. Jazaieri H, Goldin PR, Werner K, Ziv M, Gross JJ. A randomized trial of MBSR versus aerobic exercise for social anxiety disorder. J Clin Psychol. 2012;68(7):715–31.

54. Jezova D, Makatsori A, Duncko R, Moncek F, Jakubek M. High trait anxiety in healthy subjects is associated with low neuroendocrine activity during psychosocial stress. Prog Neuro-Psychopharmacol Biol Psychiatry. 2004;28(8):1331–6.

55. Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain, and illness., 15th anniversary ed. New York: Delta Trade Paperback/Bantam Dell; 2005.

56. Kabat-Zinn J, Massion AO, Kristeller J, Peterson LG, Fletcher KE, Pbert L, Lenderking WR, Santorelli SF. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. Am J Psychiatry. 1992;149(7):936–43.

57. Kaduskar P, Suryanarayana KM. Yoga: an endocrine therapy. Indian J Endocrinol Metab. 2015;19(3):437–8.

58. Katzman MA, Vermani M, Gerbarg PL, Brown RP, Iorio C, Davis M, Cameron C, Tsirgielis D. A multicomponent yoga-based, breath intervention program as an adjunctive treatment in patients suffering from generalized anxiety disorder with or without comorbidities. Int J Yoga. 2012;5(1):57–65.

59. Keith VM, Kronenfeld JJ, Rivers PA, Liang SY. Assessing the effects of race and ethnicity on use of complementary and alternative therapies in the USA. Ethn Health. 2005;10(1):19–32.

60. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005a;62(6):593–602.

61. Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, Wang P, Wells KB, Zaslavsky AM. Prevalence and treatment of mental disorders, 1990 to 2003. N Engl J Med. 2005b;352(24):2515–23.

62. Khan A, Leventhal RM, Khan S, Brown WA. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. J Affect Disord. 2002;68(2–3):183–90.

63. Khoury B, Lecomte T, Fortin G, Masse M, Therien P, Bouchard V, Chapleau MA, Paquin K, Hofmann SG. Mindfulness-based therapy: a comprehensive meta-analysis. Clin Psychol Rev. 2013;33(6):763–71.

64. Kim B, Lee SH, Kim YW, Choi TK, Yook K, Suh SY, Cho SJ, Yook KH. Effectiveness of a mindfulness-based cognitive therapy program as an adjunct to pharmacotherapy in patients with panic disorder. J Anxiety Disord. 2010;24(6):590–5.

65. Koszycki D, Benger M, Shlik J, Bradwejn J. Randomized trial of a meditation-based stress reduction program and cognitive behavior therapy in generalized social anxiety disorder. Behav Res Ther. 2007;45(10):2518–26.

66. Ludwig DS, Kabat-Zinn J. Mindfulness in medicine. JAMA. 2008;300(11):1350–2.

67. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HM, Chen G, McClure-Tone EB, Ernst M, Pine DS. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry. 2008;65(5):568–76.

68. National_Center_for_Complementary_and_Integrative_Health. Massage therapy. 2016. Retrieved April 16, 2019, from https://nccih.nih.gov/health/massage

69. Nepon J, Belik SL, Bolton J, Sareen J. The relationship between anxiety disorders and suicide attempts: findings from the National Epidemiologic Survey on alcohol and related conditions. Depress Anxiety. 2010;27(9):791–8.

70. NICE. Generalised anxiety disorder in adults: management in primary, secondary and community care. Leicester: British Psychological Society; 2011.

71. Nyer M, Nauphal M, Roberg R, Streeter C. Applications of yoga in psychiatry: what we know. Focus. 2018;16(1):12–8.

72. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci. 2005;9(5):242–9.

73. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage. 2004;23(2):483–99.

74. Ormel J, VonKorff M, Ustun TB, Pini S, Korten A, Oldehinkel T. Common mental disorders and disability across cultures. Results from the WHO collaborative study on psychological problems in general health care. JAMA. 1994;272(22):1741–8.

75. Ortner CNM, Kilner SJ, Zelazo PD. Mindfulness meditation and reduced emotional interference on a cognitive task. Motiv Emot. 2007;31(4):271.
76. Ospina MB, Bond K, Karkhaneh M, Tjosvold L, Vandermeer B, Liang Y, Bialy L, Hooton N, Buscemi N, Dryden DM, Klassen TP. Meditation practices for health: state of the research. Evid Rep Technol Assess (Full Rep). 2007;Jun(155):1–263.
77. Park ER, Traeger L, Vranceanu AM, Scult M, Lerner JA, Benson H, Denninger J, Fricchione GL. The development of a patient-centered program based on the relaxation response: the relaxation response resiliency program (3RP). Psychosomatics. 2013;54(2):165–74.
78. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol Psychiatry. 2005;57(3):210–9.
79. Piet J, Hougaard E, Hecksher MS, Rosenberg NK. A randomized pilot study of mindfulness-based cognitive therapy and group cognitive-behavioral therapy for young adults with social phobia. Scand J Psychol. 2010;51(5):403–10.
80. Porensky EK, Dew MA, Karp JF, Skidmore E, Rollman BL, Shear MK, Lenze EJ. The burden of late-life generalized anxiety disorder: effects on disability, health-related quality of life, and healthcare utilization. Am J Geriatr Psychiatry. 2009;17(6):473–82.
81. Ranjbar F, Hemmati L, Rezaei S. P03-511 – the effects of yoga in women with generalized anxiety disorder. Eur Psychiatry. 2011;26(S1):1681.
82. Rapaport MH, Schettler P, Larson ER, Edwards SA, Dunlop BW, Rakofsky JJ, Kinkead B. Acute Swedish massage monotherapy successfully remediates symptoms of generalized anxiety disorder: a proof-of-concept, randomized controlled study. J Clin Psychiatry. 2016;77(7):e883–91.
83. Santana L, Fontenelle LF. A review of studies concerning treatment adherence of patients with anxiety disorders. Patient Prefer Adherence. 2011;5:427–39.
84. Sartorius A, Kiening KL, Kirsch P, von Gall CC, Haberkorn U, Unterberg AW, Meyer-Lindenberg A. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. Biological psychiatry. 2010;67(2):e9–e11.
85. Segal ZV, Williams JMG, Teasdale JD. Mindfulness-based cognitive therapy for depression: a new approach to preventing relapse. New York: Guilford Press; 2002.
86. Shapero BG, Greenberg J, Pedrelli P, de Jong M, Desbordes G. Mindfulness-based interventions in psychiatry. Focus (Am Psychiatr Publ). 2018;16(1):32–9.
87. Sherman KJ, Ludman EJ, Cook AJ, Hawkes RJ, Roy-Byrne PP, Bentley S, Brooks MZ, Cherkin DC. Effectiveness of therapeutic massage for generalized anxiety disorder: a randomized controlled trial. Depress Anxiety. 2010;27(5):441.
88. Smith C, Hancock H, Blake-Mortimer J, Eckert K. A randomised comparative trial of yoga and relaxation to reduce stress and anxiety. Complement Ther Med. 2007;15(2):77–83.
89. Stein MB, Cantrell CR, Sokol MC, Eaddy MT, Shah MB. Antidepressant adherence and medical resource use among managed care patients with anxiety disorders. Psychiatr Serv. 2006;57(5):673–80.
90. Strauss C, Cavanagh K, Oliver A, Pettman D. Mindfulness-based interventions for people diagnosed with a current episode of an anxiety or depressive disorder: a meta-analysis of randomised controlled trials. PLoS One. 2014;9(4):e96110.
91. Streeter CC, Gerbarg PL, Saper RB, Ciraulo DA, Brown RP. Effects of yoga on the autonomic nervous system, gamma-aminobutyric-acid, and allostasis in epilepsy, depression, and post-traumatic stress disorder. Med Hypotheses. 2012;78(5):571–9.
92. Sylvia LG, Bui E, Baier AL, Mehta DH, Denninger JW, Fricchione GL, Casey A, Kagan L, Park ER, Simon NM. Resilient warrior: a stress management group to improve psychological health in service members. Glob Adv Health Med. 2015;4(6):38–42.
93. Teasdale JD, Moore RG, Hayhurst H, Pope M, Williams S, Segal ZV. Metacognitive awareness and prevention of relapse in depression: empirical evidence. Journal of consulting and clinical psychology. 2002;70(2):275.
94. Thurston MD, Goldin P, Heimberg R, Gross JJ. Self-views in social anxiety disorder: the impact of CBT versus MBSR. J Anxiety Disord. 2017;47:83–90.

95. Uebelacker LA, Broughton MK. Yoga for depression and anxiety: a review of published research and implications for healthcare providers. R I Med J (2013). 2016;99(3):20–2.
96. Vaccarino O, Levitan R, Ravindran A. The cortisol response to social stress in social anxiety disorder. Asian J Psychiatr. 2015;14:57–60.
97. Vago DR, Silbersweig DA. Self-awareness, self-regulation, and self-transcendence (S-ART): a framework for understanding the neurobiological mechanisms of mindfulness. Front Hum Neurosci. 2012;6:296.
98. Van Etten ML, Taylor S. Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. Clin Psychol Psychother. 1998;5(3):126–44.
99. Veenstra L, Schneider IK, Koole SL. Embodied mood regulation: the impact of body posture on mood recovery, negative thoughts, and mood-congruent recall. Cogn Emot. 2017;31(7):1361–76.
100. Vollestad J, Nielsen MB, Nielsen GH. Mindfulness- and acceptance-based interventions for anxiety disorders: a systematic review and meta-analysis. Br J Clin Psychol. 2012;51(3):239–60.
101. Vorkapic CF, Range B. Reducing the symptomatology of panic disorder: the effects of a yoga program alone and in combination with cognitive-behavioral therapy. Front Psych. 2014;5:177.
102. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-subcortical pathways mediating successful emotion regulation. Neuron. 2008;59(6):1037–50.
103. Walther A, Lacker TJ, Ehlert U. Everybody was Kung-Fu fighting-the beneficial effects of Tai Chi Qigong and self-defense Kung-Fu training on psychological and endocrine health in middle aged and older men. Complement Ther Med. 2018;36:68–72.
104. Wang F, Lee E-KO, Wu T, Benson H, Fricchione G, Wang W, Yeung AS. The effects of tai chi on depression, anxiety, and psychological well-being: a systematic review and meta-analysis. Int J Behav Med. 2014;21(4):605–17.
105. Wang WC, Zhang AL, Rasmussen B, Lin LW, Dunning T, Kang SW, Park BJ, Lo SK. The effect of Tai Chi on psychosocial well-being: a systematic review of randomized controlled trials. J Acupunct Meridian Stud. 2009;2(3):171–81.
106. Wilkes C, Kydd R, Sagar M, Broadbent E. Upright posture improves affect and fatigue in people with depressive symptoms. J Behav Ther Exp Psychiatry. 2017;54:143–9.
107. Wong SY, Yip BH, Mak WW, Mercer S, Cheung EY, Ling CY, Lui WW, Tang WK, Lo HH, Wu JC, Lee TM, Gao T, Griffiths SM, Chan PH, Ma HS. Mindfulness-based cognitive therapy v. group psychoeducation for people with generalised anxiety disorder: randomised controlled trial. Br J Psychiatry. 2016;209(1):68–75.
108. Xiong GL, Doraiswamy PM. Does meditation enhance cognition and brain plasticity? Ann N Y Acad Sci. 2009;1172:63–9.
109. Yeh GY, Wang C, Wayne PM, Phillips RS. The effect of tai chi exercise on blood pressure: a systematic review. Prev Cardiol. 2008;11(2):82–9.
110. Zou L, Sasaki JE, Wei GX, Huang T, Yeung AS, Neto OB, Chen KW, Hui SS. Effects of mind(−)body exercises (tai chi/yoga) on heart rate variability parameters and perceived stress: a systematic review with meta-analysis of randomized controlled trials. J Clin Med. 2018;7(11) https://doi.org/10.3390/jcm7110404.

Chapter 15
Transcranial Photobiomodulation for Anxiety Disorders and Post-traumatic Stress Disorder

Marco Antonio Caldieraro, Marco Maiello, Olivia Losiewicz, and Paolo Cassano

Introduction

Photobiomodulation (PBM), also called "low-level light therapy" or "low-level laser therapy," is a novel device-based treatment under development for different neuropsychiatric disorders [21]. PBM uses low-level lasers (LLL) or light-emitting diodes (LEDs) to deliver near-infrared (NIR) or red light aiming to modulate metabolism and functioning of different tissues and organs, including the brain [12]. Biological activity has also been reported for other wavelengths in vitro [57]; however, the research on PBM has focused on NIR because light in this range has better tissue penetration and a well-known photoacceptor, the mitochondrial enzyme cytochrome c oxidase (CCO) [15].

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PBM is noninvasive, and NIR is a nonionizing electromagnetic irradiation that is absorbed by endogenous chromophores and is minimally dissipated as thermal energy [39]. The suggested primary mechanism of action of PBM using NIR is the enhancement of mitochondrial bioenergetics metabolism via the delivery of energy to the CCO and increased adenosine triphosphate (ATP) production. Mitochondrial dysfunction is associated with anxiety [18], and mitochondrial targets are proposed for pharmacological anxiolytic treatments [43, 55].

Most of the research on PBM for neuropsychiatric disorders focuses on transcranial PBM (t-PBM). This modality delivers NIR to the scalp, aiming to directly modulate areas of the brain cortex subjacent to the stimulation spot [51]. However, psychological effects of indirect or systemic PBM (s-PBM) have also been postulated [54]. In the s-PBM modality, the light can be delivered intranasally or transcutaneously to other parts of the body (i.e., not necessarily to the scalp). In this case, the effect on the brain would be mediated by components of peripheral tissues, such as blood cells [24].

History

In 1965, McGuff and collaborators reported an antitumor effect of ruby lasers on human tumors implanted in hamsters and in cancer patients [36]. Two years later, Endre Mester – at the Semmelweis Medical University (Hungary) – discovered PBM, while trying to replicate the same finding in mice. Inadvertently, Mester used lasers with much lower power, when compared to those of McGuff's study and failed to replicate the antitumor effect. However, Mester observed a faster rate of hair growth in the mice treated with his low-power laser [37]. In a later study, he also reported that the same laser stimulated wound healing in rats [31]. After these initial observations on PBM, extensive research on the biological effects of NIR and red light has been performed. Currently, NIR and red light are used in the medical field for the treatment of a variety of conditions such as muscle pain [19], wounds [14], neuropathic pain [22], headache [1], periorbital wrinkles [23, 50], and alopecia [61].

The pioneer in the use of PBM to treat central nervous system (CNS) injury was Shimon Rochkind. His group demonstrated that transcutaneous NIR irradiation enhanced axonal sprouting and spinal cord repair in animal models of spinal cord injury [46–48]. Later studies showed that light delivered transcutaneously penetrates to the spine and that penetration is highest for the NIR wavelengths [2]. The use of transcranial phototherapy for treating brain disorders started with its application to acute stroke. Numerous preclinical animal studies [33, 34, 44] suggested that the application of NIR laser (810 nm) to the head after induction of an acute stroke had beneficial effects on subsequent neurological performance and reduced lesion size. These promising animal studies led to the conduction of a series of clinical trials called NeuroThera Effectiveness and Safety Trials (NEST). Altogether, three large studies were conducted with a total of 1410 acute stroke

patients [NEST-1 (*n* = 120), NEST-2 (*n* = 660), and NEST-3 (*n* = 630)] [20, 32, 62]. NEST-1 was designed to demonstrate the safety and effectiveness of a single session of t-PBM in the first 24 hours after a stroke. The group receiving the active treatment had a significantly greater improvement than the control condition (assessed by the NIH Stroke Severity Scale) at 5 and 90 days poststroke. NEST-2 reported benefit of active t-PBM over sham treatment for moderate and moderate-to-severe stroke, but not for severe stroke. Despite promising results in the initial trials, the NEST-3 failed to replicate any clinical benefits for one session of PBM after acute stroke. There is no consensus on the literature to explain the discrepancies between the results of NEST-3 and the previous two trials. However, suggestions for future trials emerged, such as using higher power, multiple sessions, and initiating the treatment in the first hours after the stroke [21]. Of note, the NEST trials demonstrated that NIR light (810 nm) delivered transcranially with a class-IV laser was safe, with no significant differences in rates of adverse events when compared to sham (simulated) exposure. Other preclinical studies and clinical trials have suggested that transcranial PBM is safe and effective in reducing brain lesion volume, reducing inflammation, stimulating neurogenesis, and enhancing learning, memory, and executive functioning in acute [3, 25, 58–60] and chronic [40–42] traumatic brain injury (TBI) and has beneficial effects on neurodegenerative diseases including Alzheimer's and Parkinson's diseases [17, 45] and depressive disorders [7].

The Potential of Transcranial Photobiomodulation for the Anxious

Standard treatments for anxiety disorders and PTSD are medication and psychotherapy, and most first-line treatment medication for these disorders are antidepressants [4]. Treatment resistance is a problem for a significant number of patients with anxiety disorders or post-traumatic stress disorder (PTSD) receiving standard treatments [4]. Beyond the limitations in efficacy, medications and psychotherapies for anxiety have other shortcomings. Pharmacological treatments present burdensome side effects [11], and evidence-based psychotherapy requires frequent sessions and specialized professionals; therefore, access is limited.

The significant proportion of anxiety disorders and PTSD patients who do not respond to or tolerate standard treatments indicate the need for new therapies. For other psychiatric disorders, such as major depressive disorder (MDD), device-based treatments can be offered. Those include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), magnetic seizure therapy (MST), and deep brain stimulation (DBS) [38]. However, there are no device-based treatment approved for anxiety or PTSD.

Although research on t-PBM for anxiety disorders is still preliminary – especially in regard to its efficacy – this modality is a promising new treatment. So far,

t-PBM has not been associated with either sexual side effects, weight gain, or cognitive disturbances, which are instead frequent limitation to the long-term use of antidepressant medication. Since, self-administration at home of t-PBM is considered safe, since its cost and time demands are modest when compared to evidence-base psychotherapy, if effective and well tolerated, t-PBM could become a widely accessible intervention for the acute treatment, continuation, and maintenance of anxiety disorders, scalable to the needs of the United States.

Current Evidence

The effects of t-PBM on anxiety and PTSD were studied in clinical and preclinical studies.

Using a rat model, Rojas et al. studied t-PBM with red light (660 nm) delivered by a LED device (LEDtronics, Inc., Torrance, CA) for anxiety and post-traumatic syndromes [49]. The device power density was 9 mW/cm^2. First, the authors tested the effect of four energy densities (fluence) ranging from 5.4 J/cm^2 (10 min) to 21.6 J/ cm^2 (40 min) and reported that fear extinction improved with the lower dose and worsened with the highest dose. In a second experiment, they tested only the low dose (5.4 J/cm^2) t-PBM after fear extinction and found that this treatment prevented fear renewal [49].

Schiffer et al. studied the effect of a single session of t-PBM on ten participants with MDD using an LED instrument (Marubeni America Corp.) [52]. The NIR was delivered on EEG sites F3 and F4, which cover the dorsolateral prefrontal cortex (DLPFC) bilaterally. The stimulation parameters were wavelength 810 nm, irradiance 250 mW/cm^2, and fluence 60 J/cm^2, time 4 min per site. Nine of the ten participants also had a comorbid anxiety disorder, and the authors studied the effect of t-PBM on the anxiety symptoms, assessed by the Hamilton Anxiety Scale (HAM-A). The lowest symptom scores occurred 2 weeks post-treatment when mean HAM-A decreased 14.9 ± 9.6 points from baseline ($p = 0.002$). At week 4, mean HAM-A was still significantly lower than baseline scores ($p = 0.008$) – with a decrease of 9.0 ± 7.5 points from baseline – but significantly higher than at week 2 ($p = 0.004$) [52]. Results on depressive symptoms were similar, with lowest scores on the HAM-D at week 2 and higher HAM-D scores at week 4 post-treatment but still lower than pre-treatment scores. This study suggests that, like for depressive symptoms, the efficacy on anxiety after a single session of t-PBM is transient.

In an open study, 11 patients with mild chronic traumatic brain injury were treated with 18 sessions of t-PBM. Four of the 11 participants met diagnostic criteria for PTSD [42]. During each session (three times a week for 6 weeks), the light was delivered to 11 sites on the scalp (22.5 cm^2 each) placed throughout the midline and bilaterally on frontal, parietal, and temporal areas. The treatment used a combination of NIR (870 nm) and red light (633 nm) emitted by a LED device (MedX Health Model 1100). The total duration of each treatment session was 20 min, with light being delivered to six sites for 10 min at one time and then to the other five

sites for 10 min. The treatment parameters were power 0.5 W, irradiance 22.2 mW/ cm^2, and a fluence of 13.2 J/ cm^2, with a total energy of 3.26 kJ per session. The four participants with comorbid PTSD presented a remarkable, average reduction on the PCL-C (PTSD Checklist-Civilian) scores of 21 (range 9–30).

A group providing t-PBM for patients with different neuropsychiatric conditions reported over 50 patients treated for PTSD. According to the authors, virtually all patients presented a remarkable clinically meaningful improvement in their emotional stability and quality of life, as assessed by standardized instruments (Stephan et al., personal communication).

Da Silva et al. performed a clinical trial to assess the efficacy of PBM, exercise training, or both, as an add-on to pharmacological treatment in patients with fibromyalgia [16]. The device used for this study (Pain Away/PainCure™ nine-diode cluster device – Multi Radiance Medical®, Solon, OH, USA) combines one NIR laser beam (905 nm), four red light LEDs (640 nm), and four NIR LEDs (875 nm). The treatment consisted on 10 weeks of twice-a-week sessions (active PBM, sham PBM + exercise, active PBM + exercise, or control/sham PBM and no exercise). Each of these treatment groups comprised 20 participants. The PBM treatment was delivered to ten tender points, including one in the head (the temporomandibular joint). Each point was irradiated for 300 s, and a 39.3 J total energy per session was delivered to each point. Anxiety was assessed by the anxiety item of the Fibromyalgia Impact Questionnaire. After 10 weeks, the three treatment groups presented an improvement on anxiety significantly higher than that observed in the control group. The improvement was similar in the PBM and exercise group, and the combined treatment was superior to each of them individually.

A clinical trial on temporomandibular disorder (TMD) randomized 51 patients to receive PBM, manual therapy (a modality of physiotherapy), or both [6]. As a secondary outcome, the effect of these treatments on anxiety was assessed by the Beck depression inventory (BDI). The PBM treatment used a laser NIR device (MMOptics Recover, São Paulo, Brazil), and the treatment was delivered to five points in the temporomandibular joint (TMJ) region and to seven points in muscles related to the TMJ. Treatment was delivered three times a week for 4 weeks with the following parameters: stimulation window 0.03 cm^2, power output of 100 mW, irradiance of 3.33 W/cm^2, fluence of 133 J/cm^2, 40 s exposure time per point, and 4 J of total energy per point. A significant improvement on anxiety was observed in the three treatment groups.

Our group, at Massachusetts General Hospital, performed a pilot study to test the anxiolytic effect of t-PBM with near-infrared light in subjects suffering from generalized anxiety disorder [35]. Fifteen subjects, recruited for an 8-week study, self-administered t-PBM (830 nm) daily, for 20 min. At each treatment session, NIR was administered to the forehead bilaterally using an LED-cluster headband (Cerebral Sciences) with the following treatment parameters: NIR irradiance 30 mW/cm^2 and fluence 36 J/cm^2, for a total NIR energy of 2.9 kJ per session. The anxiety severity, assessed by the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A, [53]), decreased from 16.75 ± 5.14 to 6.83 ± 3.79 at endpoint (interim analysis in completers; $n = 12$ $p < 0.001$). Despite the small sample, the observed
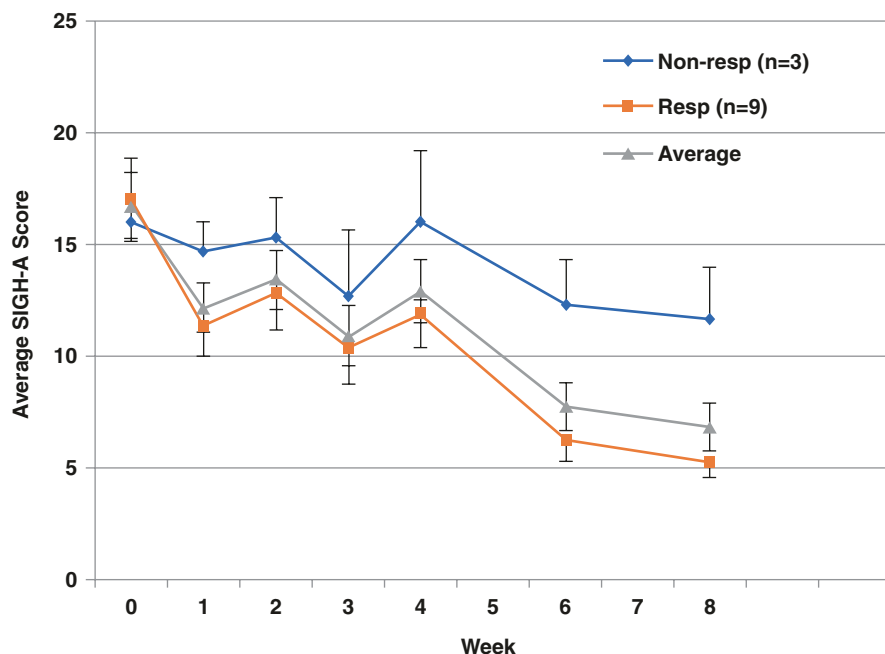
Fig. 15.1 Lighten-GAD pilot study (interim analysis): average, weekly SIGH-A scores in completers on open, daily, self-administered t-PBM

effect size was large (Cohen's d effect size = 1.70). Figure 15.1 displays the average, weekly SIGH-A scores for completers.

Little is known about the long-term anxiolytic effects of PBM. Our group reported the case of a patient receiving PBM for 31 months, as an add-on to antidepressant medication to treat depression with anxious distress [8]. The treatment was started with intranasal PBM, and t-PBM was added in the last 9 months. The treatment was well tolerated, and a continuous improvement in the anxious symptoms was observed during the overall treatment follow-up, with a more pronounced improvement in depression observed after the addition of the t-PBM. Although this is a single case study, it suggests that frequent sessions of PBM might be effective for anxious symptoms in the maintenance phase.

These studies on t-PBM for anxiety and PTSD have limitations due to their small sample sizes. Moreover, only few studies enrolled patients with a primary diagnosis of an anxiety disorder; conversely, in most studies, anxiety was not the primary outcome. These limitations temper our enthusiasm, despite the promising results reported so far. In terms of magnitude of the anxiolytic effect, these initial reports suggest that the therapeutic effects of t-PBM on anxiety and on post-traumatic stress could be even greater than on depression. This could be particularly relevant for patients suffering from PTSD, since in many cases, available pharmacological treatments produce only modest improvements. The reported clinical studies on t-PBM for anxiety used NIR or NIR + red light delivered by laser and LED devices. The

placement of the devices aimed to stimulate forebrain, parietal, and temporal areas. Therefore, current evidence supports an anxiolytic effect of t-PBM only for the stimulation at these sites. However, penetration of light could be higher when light is delivered to other parts of the scalp, such as the occipital skull [27]. New studies should answer if t-PBM directly targeting other brain areas is also associated with an anxiolytic effect. Also, comparative studies of t- and s-PBM would be beneficial, since preliminary evidence suggests the systemic modality might also be effective for anxiety. Current studies also suggest that multiple and ongoing sessions might be necessary to sustain the anxiolytic effect of PBM.

Safety and Tolerability of Transcranial Photobiomodulation

Except for laser devices (class 3–4) for which accidental light exposure of the retina might result in severe injury to the macula, devices used for PBM are typically categorized as nonsignificant risk devices by the FDA and are available over the counter, but not for psychiatric indications per se. Also, there is a negligible risk of interaction with medications, except for light-activated drugs such as cancer photosensitive chemotherapy (photodynamic therapy).

The strongest evidence on the safety of t-PBM comes from three large studies on stroke, the NEST trials, with a pooled sample of $n = 1410$ participants [20, 26, 32]. These trials assessed the therapeutic and side effects of one session of transcranial NIR (808 nm) in the first 24 hours after a stroke. Overall, no significant differences in the rates of adverse effects were observed between groups: active versus sham (simulated) treatment.

The clinical studies on t-PBM for MDD also indicate that treatment is safe and well tolerated by depressed patients. Two uncontrolled studies using one and six sessions of t-PBM reported no side effects associated with treatment [9, 52]. A clinical trial of 16 sessions observed more side effects in the active treatment group; however, statistical significance was not assessed due to the small sample size [13]. Although no serious adverse events were observed, the most frequent adverse effects were headaches, insomnia, illusions – such as seeing vivid colors or "tasting from an ashtray" – and irritable mood.

Similarly, no serious adverse events were reported in the studies assessing t-PBM for anxiety or for PTSD. The study reported by Schiffer et al. reported no adverse events or side effects after a detailed questioning of the patients [52]. In the case report of long-term use of PBM for MDD with anxious distress, the patient presented headaches apparently associated with the treatment [8].

Interestingly, a trial on t-PBM for MDD reported an improvement of sexual dysfunction symptoms in the group receiving the active treatment [10]. If confirmed in larger trials, this would be a significant strength of t-PBM since sexual dysfunction is a common side effect of most antidepressant medications, which are used to treat not only depression but also anxiety. Moreover, cognition is frequently impaired in patients with anxiety disorders; unfortunately, current treatments have little or no

effects on this symptom, and at times they induce worsening – particularly the benzodiazepines. In turn, treatment with t-PBM was shown to exert pro-cognitive effects in healthy subjects [5].

Dosing Transcranial Photobiomodulation for Anxiety Disorders

t-PBM is not yet an evidence-based treatment for anxiety disorders. Therefore, t-PBM should be reserved for patients who either have not responded to or not tolerated approved therapies. Because of the low risk of t-PBM and alternative mechanism of action, it is considered safe both in monotherapy and in adjunction to antianxiety medications and psychotherapies. t-PBM could also be offered as an alternative modality of treatment in anxious patients who would otherwise go untreated, due to their declining evidence-based interventions.

There is no consensus on the effective and well-tolerated dose of NIR or red light in t-PBM for anxiety disorders, mostly due to the lack of data comparing different doses of t-PBM. Yet, because so little is known about the therapeutic doses of t-PBM, there is a great likelihood for ongoing and future clinical trial to be underdosed or overdosed: meaning that subtherapeutic or poorly tolerated doses might be used. The risks for the patients in the setting of a clinical trial are controlled and still minimal; however, for the field of t-PBM, there is a risk of premature conclusions on the efficacy and tolerability of this intervention. We should instead acknowledge the likelihood of negative trials where t-PBM does not show superiority to placebo. Both pharmacological and device-based interventions, which have gained FDA approval for mood and anxiety disorders, have typically done so despite several negative trials. Not surprisingly, given the challenges of dose finding and of placebo response in psychiatry, less than 50% of placebo-controlled trials on antidepressant medications have demonstrated superiority of their studied intervention [28–30]. In light of the lack of current evidence base, and of the challenges ahead for the field of t-PBM, we hereby offer some clinically informed and yet unproven observations on the dosing of t-PBM, which might inform treatment decisions in future studies:

– In the acute phase of treatment for anxiety disorders, t-PBM sessions with FDA-cleared devices are typically started with once-a-week or twice-a-week frequency and gradually increased to three to four times a week and possibly daily based on clinical response and as tolerated.
– In the continuation and maintenance phase of treatment, when t-PBM sessions are decreased to once every 2 weeks, symptoms tend to reoccur. In some cases, even lowering to once-a-week sessions might precipitate a syndrome relapse.
– Because penetration of red and NIR t-PBM hinges on multiple somatic characteristics and because individual differences are expected and because therapeutic

effects typically require weeks to manifest, defining the optimal dose is challenging. A potential strategy to identify the therapeutic dose is to titrate the dose of each session or the number of weekly sessions up to the induction of mild side effects, such as transient headaches or mild irritability.

– Elderlies might need higher doses with daily sessions and even at times twice daily sessions, possibly due to larger subarachnoid space, due to lower hydration of tissues and to brain atrophy (decreased neuronal density).

– Children might respond to lower doses both in terms of energy delivered per session and in terms of total number of sessions. They might need as little as half the number of sessions compared to adults. In preteen, young children a quarter of the adult dose per session is a reasonable starting dose. Children have less intervening tissues between skin and brain (in accordance to their stage of physical development) and higher neuronal density [56].

– While comparing different t-PBM devices, it is useful to refer to the total energy delivered per session and per week at skin level. Some devices with low irradiance (e.g., 15 mW/cm^2) are surprisingly still effective, if used on large surfaces of skin, for fairly long session (e.g., 40 min) and frequently during the week. This suggests that cumulative effects of t-PBM might be at play in determining a therapeutic response.

– Clinician should resist the temptation to conceptualize t-PBM as a single treatment modality. It is very much possible that based on chosen parameters, the primary mechanism of action for neuromodulation changes. It is possible that at very low dose, t-PBM acts by inducing electromagnetic fields near to the brain rather than delivering photon energy to the brain.

– It is unclear if the chosen sites of the source of t-PBM on the scalp and on the forehead matter in patients with anxiety disorders. However, it is expected that depending on the localization on the scalp, different cortical areas will be preferentially irradiated. The F3 and F4 sites will preferentially serve to irradiate the DLPFC; Fp1-Fpz-Fp2 instead will allow preferential irradiation of the ventromedial prefrontal cortex.

Conclusions

The treatment with t-PBM has the potential to become an effective, safe, and widely available treatment for anxiety disorders and PTSD. It has a novel mechanism of action; it is easy to administer and inexpensive. However, clinical research on t-PBM is still preliminary, and current evidence is not enough to consider it a standard treatment for these disorders. More studies are necessary to adequately test the efficacy of this treatment and to define the optimal stimulation parameters. Some of these studies are already being performed and will contribute to clarify the role of t-PBM in clinical practice.

References

1. Allais G, De Lorenzo C, Quirico PE, Lupi G, Airola G, Mana O, Benedetto C. Non-pharmacological approaches to chronic headaches: transcutaneous electrical nerve stimulation, lasertherapy and acupuncture in transformed migraine treatment. Neurol Sci. 2003;24(Suppl 2):S138–42.

2. Anders JJ. The potential of light therapy for central nervous system injury and disease. Photomed Laser Surg. 2009;27:379–80.

3. Ando T, Xuan W, Xu T, Dai T, Sharma SK, Kharkwal GB, Huang Y-Y, Wu Q, Whalen MJ, Sato S, Obara M, Hamblin MR. Comparison of therapeutic effects between pulsed and continuous wave 810-nm wavelength laser irradiation for traumatic brain injury in mice. PLoS One. 2011;6:e26212.

4. Bandelow B, Zohar J, Hollander E, Kasper S, Möller HJ, WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disoders, Zohar J, Hollander E, Kasper S, Möller HJ, Bandelow B, Allgulander C, Ayuso-Gutierrez J, Baldwin DS, Buenvicius R, Cassano G, Fineberg N, Gabriels L, Hindmarch I, Kaiya H, Klein DF, Lader M, Lecrubier Y, Lépine JP, Liebowitz MR, Lopez-Ibor JJ, Marazziti D, Miguel EC, Oh KS, Preter M, Rupprecht R, Sato M, Starcevic V, Stein DJ, van Ameringen M, Vega J. World Federation of Societies of biological psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. World J Biol Psychiatry. 2008;9(4):248–312.

5. Barrett DW, Gonzalez-Lima F. Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. Neuroscience. 2013;230:13–23.

6. Brochado FT, de Jesus LH, Carrard VC, Freddo AL, Chaves KD, Martins MD. Comparative effectiveness of photobiomodulation and manual therapy alone or combined in TMD patients: a randomized clinical trial. Braz Oral Res. 2018;32:e50. https://doi.org/10.1590/1807-3107bor-2018.vol32.0050.

7. Caldieraro MA, Cassano P. Transcranial and systemic photobiomodulation for major depressive disorder: a systematic review of efficacy, tolerability and biological mechanisms. J Affect Disord. 2019;243:262–73. https://doi.org/10.1016/j.jad.2018.09.048.

8. Caldieraro MA, Sani G, Bui E, Cassano P. Long-term near-infrared photobiomodulation for anxious depression complicated by Takotsubo cardiomyopathy. J Clin Psychopharmacol. 2018;38:1. https://doi.org/10.1097/jcp.0000000000000883.

9. Cassano P, Cusin C, Mischoulon D, Hamblin MR, De Taboada L, Pisoni A, Chang T, Yeung A, Ionescu DF, Petrie SR, Nierenberg AA, Fava M, Iosifescu DV. Near-infrared transcranial radiation for major depressive disorder: proof of concept study. Psychiatry J. 2015;2015:352979.

10. Cassano P, Dording C, Thomas G, Foster S, Yeung A, Uchida M, Hamblin M, Bui E, Fava M, Mischoulon D, Iosifescu DV. Effects of transcranial photobiomodulation with near-infrared light on sexual dysfunction. Lasers Surg Med. 2018a;51(2):127–35.

11. Cassano P, Fava M. Tolerability issues during long-term treatment with antidepressants. Ann Clin Psychiatry. 2004;16:15–25.

12. Cassano P, Petrie SR, Hamblin MR, Henderson TA, Iosifescu DV. Review of transcranial photobiomodulation for major depressive disorder: targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. Neurophotonics. 2016;3:031404.

13. Cassano P, Petrie SR, Mischoulon D, Cusin C, Katnani H, Yeung A, De Taboada L, Archibald A, Bui E, Baer L, Chang T, Chen J, Pedrelli P, Fisher L, Farabaugh A, Hamblin M, Alpert J, Fava M, Iosifescu DV. Transcranial Photobiomodulation for the treatment of major depressive disorder. The ELATED-2 pilot trial. Photomed Laser Surg. 2018b;4490.

14. Chaves ME d A, de Araújo AR, Piancastelli ACC, Pinotti M. Effects of low-power light therapy on wound healing: LASER x LED. An Bras Dermatol. 2014;89:616–23.

15. Chung H, Dai T, Sharma SK, Huang Y-Y, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng. 2012;40:516–33.

16. da Silva MM, Albertini R, de Tarso Camillo de Carvalho P, Leal-Junior ECP, Bussadori SK, Vieira SS, Bocalini DS, de Oliveira LVF, Grandinetti V, Silva JA, Serra AJ. Randomized, blinded, controlled trial on effectiveness of photobiomodulation therapy and exercise training in the fibromyalgia treatment. Lasers Med Sci. 2018;33:343–51. https://doi.org/10.1007/s10103-017-2388-2.

17. De Taboada L, Yu J, El-Amouri S, Gattoni-Celli S, Richieri S, McCarthy T, Streeter J, Kindy MS. Transcranial laser therapy attenuates amyloid-β peptide neuropathology in amyloid-β protein precursor transgenic mice. J Alzheimers Dis. 2011;23:521–35.

18. Fedoce A d G, Ferreira F, Bota RG, Bonet-Costa V, Sun PY, Davies KJA. The role of oxidative stress in anxiety disorder: cause or consequence? Free Radic Res. 2018;52:737. https://doi.org/10.1080/10715762.2018.1475733.

19. Ferraresi C, Hamblin MR, Parizotto NA. Low-level laser (light) therapy (LLLT) on muscle tissue: performance, fatigue and repair benefited by the power of light. Photonics Lasers Med. 2012;1:267–86.

20. Hacke W, Schellinger PD, Albers GW, Bornstein NM, Dahlof BL, Fulton R, Kasner SE, Shuaib A, Richieri SP, Dilly SG, Zivin J, Lees KR, NEST 3 Committees and Investigators. Transcranial laser therapy in acute stroke treatment: results of neurothera effectiveness and safety trial 3, a phase III clinical end point device trial. Stroke. 2014;45:3187–93.

21. Hamblin MR. Shining light on the head: Photobiomodulation for brain disorders. BBA Clin. 2016;6:113–24. https://doi.org/10.1016/j.bbacli.2016.09.002.

22. Harkless LB, DeLellis S, Carnegie DH, Burke TJ. Improved foot sensitivity and pain reduction in patients with peripheral neuropathy after treatment with monochromatic infrared photo energy – MIRE. J Diabetes Complicat. 2006;20:81–7.

23. Hersant B, SidAhmed-Mezi M, Bosc R, Meningaud JP. Current indications of low-level laser therapy in plastic surgery: a review. Photomed Laser Surg. 2015;33:283–97.

24. Hroudová J, Fišar Z, Kitzlerová E, Zvěřová M, Raboch J. Mitochondrial respiration in blood platelets of depressive patients. Mitochondrion. 2013;13:795–800.

25. Huang Y-Y, Gupta A, Vecchio D, de Arce VJB, Huang S-F, Xuan W, Hamblin MR. Transcranial low level laser (light) therapy for traumatic brain injury. J Biophotonics. 2012;5:827–37.

26. Huisa BN, Stemer AB, Walker MG, Rapp K, Meyer BC, Zivin JA, NEST-1 and -2 investigators. Transcranial laser therapy for acute ischemic stroke: a pooled analysis of NEST-1 and NEST-2. Int J Stroke. 2013;8:315–20.

27. Jagdeo JR, Adams LE, Brody NI, Siegel DM. Transcranial red and near infrared light transmission in a cadaveric model. PLoS One. 2012;7:e47460.

28. Khan A, Fahl Mar K, Faucett J, Khan Schilling S, Brown WA. Has the rising placebo response impacted antidepressant clinical trial outcome? Data from the US Food and Drug Administration 1987-2013. World Psychiatry. 2017;16:181–92.

29. Khan A, Khan S, Brown WA. Are placebo controls necessary to test new antidepressants and anxiolytics? Int J Neuropsychopharmacol. 2002;5:193–7.

30. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. Arch Gen Psychiatry. 2000;57:311–7.

31. Kovács IB, Mester E, Görög P. Stimulation of wound healing with laser beam in the rat. Experientia. 1974;30:1275–6.

32. Lampl Y, Zivin JA, Fisher M, Lew R, Welin L, Dahlof B, Borenstein P, Andersson B, Perez J, Caparo C, Ilic S, Oron U. Infrared laser therapy for ischemic stroke: a new treatment strategy: results of the NeuroThera effectiveness and safety trial-1 (NEST-1). Stroke. 2007;38:1843–9.

33. Lapchak PA, Araujo DM, Hefti F. Systemic interleukin-1 beta decreases brain-derived neurotrophic factor messenger RNA expression in the rat hippocampal formation. Neuroscience. 1993;53:297–301.

34. Lapchak PA, Wei J, Zivin JA. Transcranial infrared laser therapy improves clinical rating scores after embolic strokes in rabbits. Stroke. 2004;35:1985–8.

35. Maiello M, Losiewicz OM, Bui E, Spera V, Hamblin MR, Marques L, Cassano P. Transcranial Photobiomodulation with Near-Infrared Light for Generalized Anxiety Disorder: A Pilot Study. Photobiomodulation, Photomedicine, and Laser Surgery. 2019;37(10):644–50.

36. McGuff PE, Deterling RA, Gottlieb LS. Tumoricidal effect of laser energy on experimental and human malignant tumors. N Engl J Med. 1965;273:490–2.

37. Mester E, Szende B, Gärtner P. The effect of laser beams on the growth of hair in mice. Radiobiol Radiother (Berl). 1968;9:621–6.

38. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, Modirrousta M, Patry S, Vila-Rodriguez F, Lam RW, MacQueen GM, Parikh SV, Ravindran AV, Group, C.D.W. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatr. 2016;61:561–75.

39. Mochizuki-Oda N, Kataoka Y, Cui Y, Yamada H, Heya M, Awazu K. Effects of near-infra-red laser irradiation on adenosine triphosphate and adenosine diphosphate contents of rat brain tissue. Neurosci Lett. 2002;323:207–10.

40. Naeser MA, Hamblin MR. Potential for transcranial laser or LED therapy to treat stroke, traumatic brain injury, and neurodegenerative disease. Photomed Laser Surg. 2011;29:443–6.

41. Naeser MA, Martin PI, Ho MD, Krengel MH, Bogdanova Y, Knight JA, Yee MK, Zafonte R, Frazier J, Hamblin MR, Koo B-B. Transcranial, red/near-infrared light-emitting diode therapy to improve cognition in chronic traumatic brain injury. Photomed Laser Surg. 2016;34:610–26.

42. Naeser MA, Zafonte R, Krengel MH, Martin PI, Frazier J, Hamblin MR, Knight JA, Meehan WP, Baker EH. Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: open-protocol study. J Neurotrauma. 2014;31:1008–17.

43. Nussbaumer M, Asara JM, Teplytska L, Murphy MP, Logan A, Turck CW, Filiou MD. Selective mitochondrial targeting exerts anxiolytic effects in vivo. Neuropsychopharmacology. 2016;41:1751. https://doi.org/10.1038/npp.2015.341.

44. Oron A, Oron U, Chen J, Eilam A, Zhang C, Sadeh M, Lampl Y, Streeter J, DeTaboada L, Chopp M. Low-level laser therapy applied transcranially to rats after induction of stroke significantly reduces long-term neurological deficits. Stroke. 2006;37:2620–4.

45. Purushothuman S, Johnstone DM, Nandasena C, Mitrofanis J, Stone J. Photobiomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex – evidence from two transgenic mouse models. Alzheimers Res Ther. 2014;6:2.

46. Rochkind S, Barr-Nea L, Bartal A, Nissan M, Lubart R, Razon N. New methods of treatment of severely injured sciatic nerve and spinal cord. An experimental study. Acta Neurochir Suppl (Wien). 1988;43:91–3.

47. Rochkind S, Ouaknine GE. New trend in neuroscience: low-power laser effect on peripheral and central nervous system (basic science, preclinical and clinical studies). Neurol Res. 1992;14:2–11.

48. Rochkind S, Vogler I, Barr-Nea L. Spinal cord response to laser treatment of injured peripheral nerve. Spine (Phila Pa 1976). 1990;15:6–10.

49. Rojas JC, Bruchey AK, Gonzalez-Lima F. Low-level light therapy improves cortical metabolic capacity and memory retention. J Alzheimers Dis. 2012;32:741–52.

50. Russell BA, Kellett N, Reilly LR. A study to determine the efficacy of combination LED light therapy (633 nm and 830 nm) in facial skin rejuvenation. J Cosmet Laser Ther. 2005;7:196–200.

51. Salehpour F, Rasta SH. The potential of transcranial photobiomodulation therapy for treatment of major depressive disorder. Rev Neurosci. 2017;28:441–53.

52. Schiffer F, Johnston AL, Ravichandran C, Polcari A, Teicher MH, Webb RH, Hamblin MR. Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety. Behav Brain Funct. 2009;5:46.

53. Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, et al. Reliability and validity of a structured interview guide for the Hamilton anxiety rating scale (SIGH-A). Depress Anxiety. 2001;13:166–78.
54. Sommer AP, Trelles MA. Light pumping energy into blood mitochondria: a new trend against depression? Photomed Laser Surg. 2014;32:59–60.
55. Strobbe D, Campanella M. Anxiolytic therapy: a paradigm of successful mitochondrial pharmacology. Trends Pharmacol Sci. 2018;39:437. https://doi.org/10.1016/j.tips.2018.02.008.
56. Tsujimoto S. The prefrontal cortex: functional neural development during early childhood. Neuroscientist. 2008;14:345–58.
57. Wang Y, Huang Y-Y, Wang Y, Lyu P, Hamblin MR. Photobiomodulation (blue and green light) encourages osteoblastic-differentiation of human adipose-derived stem cells: role of intracellular calcium and light-gated ion channels. Nat Publ Gr. 2016;6:33719.
58. Xuan W, Agrawal T, Huang L, Gupta GK, Hamblin MR. Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis. J Biophotonics. 2015;8:502–11.
59. Xuan W, Vatansever F, Huang L, Hamblin MR. Transcranial low-level laser therapy enhances learning, memory, and neuroprogenitor cells after traumatic brain injury in mice. J Biomed Opt. 2014;19:108003.
60. Xuan W, Vatansever F, Huang L, Wu Q, Xuan Y, Dai T, Ando T, Xu T, Huang Y-Y, Hamblin MR. Transcranial low-level laser therapy improves neurological performance in traumatic brain injury in mice: effect of treatment repetition regimen. PLoS One. 2013;8:e53454.
61. Zarei M, Wikramanayake TC, Falto-Aizpurua L, Schachner LA, Jimenez JJ. Low level laser therapy and hair regrowth: an evidence-based review. Lasers Med Sci. 2016;31:363–71.
62. Zivin JA, Albers GW, Bornstein N, Chippendale T, Dahlof B, Devlin T, Fisher M, Hacke W, Holt W, Ilic S, Kasner S, Lew R, Nash M, Perez J, Rymer M, Schellinger P, Schneider D, Schwab S, Veltkamp R, Walker M, Streeter J, NeuroThera Effectiveness and Safety Trial-2 Investigators. Effectiveness and safety of transcranial laser therapy for acute ischemic stroke. Stroke. 2009;40:1359–64.

Chapter 16
Treatment of Anxiety Disorders in the Digital Age

Check for updates

Allyson M. Blackburn and Elizabeth M. Goetter

Introduction

Anxiety is highly prevalent, and roughly one third of adults will meet criteria for a diagnosable anxiety disorder at some point in their life [1]. Despite the prevalence of anxiety disorders, only about a fifth of those will receive mental health care, and only 33.8% of participants in care receive minimally adequate treatment [2]. One study of 1636 participants found that only 19% of those who met for a probable anxiety or depressive disorder received appropriate treatment [3]. A study of adolescents aged 12–17 found that of those who met for a probable anxiety disorder, only 18.2% used any mental health services [4]. The underutilization of healthcare for people with anxiety disorders suggests that barriers exist which make treatment engagement difficult. Potential barriers include limited mental health literacy, avoidance (a core symptom feature of anxiety disorders), stigma, and logistical barriers (i.e., cost, wait times) associated with seeking care [5–7].

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Rationale for Digital Tools to Treat Anxiety Disorders

Advanced telecommunications technologies (e.g., phone, Internet-based applications with varying levels of therapist participation) are potential barrier reduction tools for anxiety disorders. Previous research has found that digital innovations are powerful tools through which to promote health and well-being across a variety of populations including those with depression [8], problematic alcohol use, late-stage bipolar disorder [9], and early psychosis [10, 11]. Along with their growing ubiquity, these digital tools provide users with a degree of privacy and anonymity, and their delivery is not contingent on the geographical location of the provider. For individuals with anxiety, some of whom have specific fears involving social evaluation or traveling far from home, or for whom avoidance is a significant barrier, technology-mediated treatments may hold particular appeal. In fact, technology-mediated treatments may also enhance engagement particularly for individuals with anxiety. For example, in a sample of 150 participants with specific phobias, patients were more likely to choose virtual reality exposure over in vivo exposure and were less likely to refuse virtual reality than in vivo exposure therapy [12]. Moreover, a significant minority (up to 43.24%) of individuals are interested in Internet-mediated treatments, especially those who cite stigma as a barrier to care [13]. As such, these are obvious methods to study for helping individuals with anxiety disorders overcome barriers to treatment [14, 15].

Digital Innovations as Tools for Psychotherapy

First, and perhaps one of the earliest technologically mediated mental health interventions, was the telephone [16]. Since then, several digital tools and technological applications have been developed as means for delivering mental health interventions. We review three broad categories of digital tools – Internet-mediated treatments, virtual reality, and mobile phone-based interventions – though these are not mutually exclusive categories. Internet-mediated interventions are a broad class of technological tools that include online self-help, videoconference and messaging-based interventions, and other web-based platforms with varying degrees of therapist support. Virtual reality interventions use real-time computer-generated images as well as tracking devices, sound displays, sensory inputs, and visual displaces to immerse patients in a computer-generated world, which, for individuals with anxiety disorders, aid in exposure therapy [17]. Finally, mobile phone-based interventions involve use of self-guided phone applications. Digital tools for the treatment of anxiety have become more popular in recent years [18, 19], targeting anxiety which is unspecified or disorder-specific, including generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder with or without agoraphobia (PD/A), obsessive compulsive disorder (OCD), and posttraumatic stress disorder (PTSD).

Internet-Mediated Therapies

Internet-mediated interventions encompass a variety of interventions delivered remotely through an Internet connection. These interventions range in the degree of therapist support and include web-based self-help and videoconference-mediated treatment.

Web-Based Self-Help Interventions

Computerized interventions are often prominently self-guided, with online lessons, online support groups, and minimal therapist interaction, with one study limiting therapist-patient interaction to no more than 10 minutes of instant messaging per patient, per week [20]. Web-based interventions for anxiety and depression have grown extremely popular, with entire mental health clinics existing online, (e.g., MindSpot clinic or Anxiety Online; [20, 21]). As has been found with depression [22], Internet-mediated treatments have been found to be generally feasible and acceptable for people with anxiety. A meta-analysis of 14 studies (pooled n = 1,480) found that web- and computer-based interventions can be efficacious in reducing symptoms of anxiety, depression, and stress [23].

Cognitive behavioral therapy (CBT) (see Chap. 12) has been adapted for use in computerized interventions. A meta-analytic review of 22 studies of computerized CBT found that Internet-delivered CBT is acceptable and effective in treating anxiety as well as depressive episodes [18]. One retrospective study completed in Denmark found that in a sample of 203 patients being treated for depression or anxiety in an iCBT clinic as part of routine care, there were significant reductions of depression and anxiety with large effect sizes [24]. One randomized controlled trial of 54 participants with anxiety completed individually tailored, Internet-based CBT, or an attention control is found significant between group effects on measures of anxiety and depression at posttreatment, 1 year, and 2 years following treatment [25]. A randomized controlled trial of Internet-delivered cognitive behavioral for social phobia with/without motivational enhancement strategies found that both groups were effective in reducing social anxiety at posttreatment with large effect sizes that were maintained at 3-month follow-up [26].

Mindfulness-based interventions for anxiety have also been successfully piloted online. For example, a study of Internet-based acceptance and commitment therapy (ACT) for health anxiety found that the majority of their patients completed the treatment modules and reported significant reductions in symptoms of health anxiety and depression and increases in quality of life and life satisfaction [27]. Another pilot intervention of ACT was effectively adapted to a web-based platform to promote mental health skills in university students and reduce symptoms of anxiety and stress [28]. A randomized controlled trial of 91 people diagnosed with an anxiety disorder comparing an unguided, Internet-based mindfulness treatment group to an

online discussion forum control group found that those in the mindfulness treatment group experienced significantly larger decreases in symptoms of anxiety, depression, and insomnia at posttreatment [29].

Finally, transdiagnostic approaches are also growing popular among web-based self-help platforms given the myriad diagnostic presentations of the potential users. A nonrandomized trial of a therapist-assisted, online program compared to treatment as usual (supportive, in-person therapy) for college students with varying presentations of anxiety found that those who accessed the online program (including education, mindfulness, and exposure modules) had greater reductions in anxiety and greater improvement in their global functioning than the treatment-as-usual group [30]. Although not delivered to a clinical population with primary anxiety disorders per se, one randomized controlled trial comparing a web-based self-help program based on the Unified Protocol to a wait-list control for adults with clinician-diagnosed mood and/or anxiety disorder found significant reductions in anxiety, anxiety sensitivity, and symptom interference and improvements in quality of life [31]. A randomized controlled trial examining the comparative efficacy of transdiagnostic vs. disorder-specific and clinician-guided vs. self-guided treatment for social anxiety in 233 patients with SAD and comorbid disorders found large symptom reductions in all four treatment groups, and there were no significant differences between transdiagnostic treatment or disorder-specific treatment of SAD and no difference between clinician-guided and self-guided disorders [32]. Another study comparing transdiagnostic treatment approaches and disorder-specific CBT for youth with SAD delivered online with therapist support found that there was significant symptom reduction at posttreatment, though the majority of users in both treatment conditions continued to meet diagnostic criteria for SAD [33]. However, due to more promising results from a randomized controlled trial, unguided CBT delivered on the Internet compared to care-as-usual for individuals with anxiety disorders (SAD, PD/A, GAD) seen in a primary care setting was more effective than care-as-usual at posttreatment for reducing symptoms of anxiety, quality of life, and satisfaction [34].

In sum, web-based interventions are appealing because they offer a mechanism for both transdiagnostic and targeted treatment approaches and make economical use of therapist time and resources. They appear to offer substantial benefits to participants with moderate anxiety who are able to engage in this material, though more studies are needed to determine the optimal level of user engagement and its relationship to outcome.

Videoconference Interventions

Videoconferencing, which uses audio and video transmission of communication over the Internet, offers patients access to mental health treatment without having to physically present in their clinician's office [14]. Videoconference-mediated interventions offer a format equivalent to face-to-face therapy, but they are deliv-

ered remotely. Although use of videoconference-based therapy has been limited given difficulties and discrepancies in insurance reimbursement, such treatment has been effectively adapted in the treatment of unspecified anxiety in various populations and has been associated with improvements in quality of life for anxious populations [35].

Videoconference-based treatments have also been studied for the delivery of specific evidence-based treatments in clinical populations. For example, in a small sample of participants with PD/A, 12 sessions of CBT delivered via videoconference was associated with significant reductions in symptoms of panic and anxiety [37]. Results from a follow-up, nonrandomized study found that telehealth users with PD/A demonstrated significantly greater reductions in panic than in-person treatment participants [38], which researchers hypothesized was due to an optimization that occurred in the Internet-mediated treatment condition due to patient preference and acceptability of this intervention modality for patients with more severe anxiety.

Therapy delivered via videoconference has also demonstrated efficacy for people with SAD. One study adapted acceptance-based behavior therapy via videoconference for 24 participants with social anxiety. Researchers found that the intervention was effective at posttreatment and 3-month follow-up and was rated as acceptable and feasible by therapists and patients alike [39]. In the case of public speaking phobia, a specific, non-generalized form of SAD, videoconference treatment has also been utilized for the delivery of group therapy with similarly encouraging results [40].

A few small studies have provided encouraging results for the treatment of OCD and related disorders via videoconference. In one of the earliest studies, Himle and colleagues presented results from three cases of individuals treated with CBT for OCD [41]. Therapeutic alliance was strong across all three cases, patients had high rates of satisfaction with the videoconference modality, and OCD symptom improvement ranged from 44% to 55% on measures of OCD symptom severity [41]. Another study of six outpatients with OCD found that exposure therapy could be successfully delivered in a hybrid format of six videoconference sessions and nine cellphone sessions over a 3-month period. Treatment was effective (participants experienced 50% or larger improvements on measures of OCD symptoms), and acceptable, with all patients rating themselves satisfied with treatment and rating that they felt that the videoconference sessions felt natural [42]. In another open trial of home-based, videoconference-mediated exposure and ritual prevention therapy for OCD, researchers found that among 11 treatment completers, feasibility and satisfaction were highly rated by patients and therapists alike and treatment was associated significant improvement in OCD symptoms with corresponding large effect sizes [23]. Another small randomized controlled trial of 20 children with tic disorders found that Comprehensive Behavior Intervention for Tics (CBIT) delivered via telehealth was comparable to CBIT delivered in a same-room therapy format [43].

Videoconference-mediated treatments have also been effectively adapted to treat PTSD, and concerted efforts have been made to disseminate evidence-based

treatments for PTSD via videoconferencing within the Veterans Administration (VA) healthcare system [44, 45]. The literature has demonstrated that evidence-based treatments for posttraumatic stress disorder (PTSD) such as prolonged exposure therapy (PE) can be effectively delivered via telehealth [46]; however, the literature on the comparative efficacy of telecare and same-room care for PE is wanting. For instance, one review noted that studies were generally underpowered and few randomized comparative studies existed [47]. However, a non-inferiority trial of cognitive processing therapy (CPT) delivered over videoconferencing found that delivery of CPT over videoconferencing was non-inferior to in-person treatment and that there were no differences between groups in therapeutic alliance, treatment compliance, and treatment satisfaction [48].

Virtual Reality-Based Therapies

Virtual reality can sometimes form the entire platform for an intervention or can be effective in augmenting same-room treatment, most notably in the use of exposure therapy [49]. Virtual reality has been a particularly promising technological advancement for exposure-based treatments of anxiety disorders because of its ability to help the user confront various sensory stimuli associated with their anxiety in a controlled and focused way. Virtual reality has demonstrated efficacy in treating specific phobias [50, 51], social phobia [52], and PTSD [53]. One small within-subject's design study found that virtual reality was at least as effective as in vivo exposure for acrophobia; however, there were only ten subjects, and all subjects received virtual reality first [50]. However, in another study of specific phobia, 75 participants with a fear of flying were randomized to virtual reality exposure therapy, standard in vivo exposure therapy, or wait-list control. Virtual reality exposure was comparable to standard in vivo exposure in both clinical, functioning, and patient satisfaction outcomes [54]. Another similarly designed study of patients with SAD randomized individuals into virtual reality, standard in vivo exposure, or wait-list control. Virtual reality was as effective as standard in vivo, and therapists found exposure treatment in the virtual reality condition to be more practical than the standard in vivo exposure [55]. While providers have advocated for the acceptability and practicality of virtual reality exposure therapy [56, 57], they also report barriers to implementation such as technological difficulty and financial burden associated with purchasing this technology [57], thus raising questions about is feasibility in real-world or community settings. Moreover, while the research surrounding virtual reality exposure therapy has been promising, the quality of the research surrounding virtual reality exposure is limited in some instances by small sample sizes and lack of randomization [58, 59].

Recent innovations in virtual reality exposure therapy have also utilized gaming technologies to treat anxiety and may hold promise in symptom reduction [60]. One study used computer-aided vicarious exposure in which participants directed an avatar to conduct contamination exposures and found significant reductions in

self-reported OCD symptoms [61]. Another study of 14 participants with social anxiety disorder found that therapists could effectively deliver an entire treatment package of acceptance-based behavior therapy via a computerized alternative reality program (Second Life) with corresponding reductions in symptoms of social anxiety disorder (SAD), as well as avoidance and disability due to SAD symptoms [62]. Gaming-based programming has been especially promising in children with anxiety, where computer and smartphone gaming have been successful in keeping children engaged in practicing skills to combat their anxiety disorders [63].

Mobile Application Interventions

Mobile phone application-based ("app") interventions, or self-guided, self-contained, interventions that can be downloaded onto a smartphone or tablet, have grown in popularity. Although their proliferation has outpaced empirical study, some mobile applications have been shown to be effective in some circumstances [64]. Mobile applications may be effective ways to reduce barriers to treatment for people with anxiety disorders, increase the use of evidence-based treatments, and enhance care after formal mental health treatment has concluded [64]. One 3-armed randomized controlled trial of 150 people with SAD found that there were no significant differences between the active (phone and computer) conditions in all social anxiety outcomes measures and that both active conditions outperformed the wait-list condition with large effect sizes [65]. While interventions for specific interventions are being adapted, transdiagnostic protocols are also being tested [66].

Smartphone-based interventions have been particularly effective for stress reduction in a variety of populations. One pilot study of a mind-body podcast program for military and veteran caregivers found reductions in perceived stress, anxiety symptoms, and depression symptoms among 55 military caregivers [67]. Another randomized controlled trial of 150 college students with elevated stress found that an Internet and smartphone stress reduction program significantly reduced perceived stress, anxiety, and depression after 7 weeks, with effects being maintained at 3-month follow-up [68]. Headspace has been a particularly popular mobile application that has shown promising reductions in perceived stress, irritability, anxiety, and some symptoms of depression [69]. A study of patients admitted to an intensive care unit found that a mobile-mindfulness app had similar efficacy to that of a therapist-led group [70] in measures of generalized anxiety, depression, and physical symptoms following their hospitalization. Another meta-analysis of three randomized controlled trials found that participants with high depression and anxiety symptom severity benefitted from mobile stress-reduction programs greatly. According to the authors of this study, including these highly burdened individuals in online stress management programs may help people who might not otherwise seek treatment enter care [66].

However, not all app-based mental health options may be ideal or evidence based. One qualitative content analysis of 61 mental health apps found that while

mental health apps generally target anxiety, mood disorders, and general well-being, apps tend to frame mental illness simply as abnormal responses to triggers and promote personal responsibility for improvement, while potentially pathologizing healthy functioning in a situation where anxiety and mood symptoms are appropriate responses to stressful situations [71]. App-based mental health interventions may not be suitable as replacement to same room, or more structured online therapy, especially for psychiatrically ill populations, but they show promise as low-intensity interventions for less severe populations and may also be an effective adjunct to psychotherapy.

Barriers to Digital Interventions for Anxiety

While Internet-mediated interventions are promising in reducing barriers to care, they are not a panacea, and there are several key challenges and considerations. Access issues remain and are impacted by provider and patient attitudes; dropout and engagement barriers; feasibility and logistic issues; ambiguous clinical practice guidelines; and potential race, age, and geographic disparities.

Attitudes Toward Internet-Mediated Interventions

While online treatments for anxiety may be helpful for people experiencing stigma regarding their mental illness, attitudes toward online mental health treatment are mixed. Many studies report positive patient attitudes about remotely delivered interventions and patients appear to appreciate the convenience of these methods [72]. However, others have found that patients have mixed [73] or even negative [74] attitudes about digital tools for delivering mental health treatment. In some cases, patients appear to be concerned with how individually tailored such interventions can be [75, 76]. However, while attitudes toward Internet-delivered mental healthcare are mixed, these attitudes are amenable to change [77], which may be a function of increased comfort with these tools.

Mental health providers also have varying attitudes about using digital tools as mechanisms for or augmentations to psychotherapy. For instance, in a study of 717 licensed psychologists and doctoral-level students, clinicians who were oriented in cognitive-behavioral, cognitive, behavioral, and systems approaches were significantly more accepting of telepsychiatry health interventions than those practicing from dynamic, analytic, or existential orientations [78]. In some cases, providers may have more negative views than patients [79]. Providers would benefit from research-informed guidelines about use in cases where there are disparate views between providers and patients, especially if this impacts therapeutic alliance, which has a demonstrated association with treatment outcomes in Internet-mediated interventions [80].

Engagement in Internet-Mediated Interventions

Optimization of treatment engagement is another important consideration in the use of Internet-mediated interventions. There is likely a dose-response relationship in the utilization of Internet-mediated treatments. Indeed, one study of patients with anxiety and depression found that patients who actively engaged in the program had better mental health outcomes at their 6-month follow-up [81]. Internet-mediated treatments lend themselves to convenience and thus may appeal to a population of individuals who have varying levels of motivation and time for treatment at the outset. Whether or not Internet-mediated treatments are preferred by individuals with significantly different levels of motivation for treatment than traditional, in-person treatment-seeking individuals is a hypothesis that remains to be adequately tested. Nonetheless, it is important to understand how passive engagement in Internet-mediated treatments affects their effectiveness. Related to concerns about suboptimal engagement, providers treating anxiety disorders also face unique challenges associated with conducting exposure therapy via the Internet. For instance, providers may need to more vigilantly attend to safety behavior engagement and possible distractions patients face when engaging in therapy from nonclinical environments (e.g., their home) [82, 83].

Like in-person treatments, premature dropout can also pose a significant challenge in Internet-mediated treatments despite their purported convenience. For example, in a study of postpartum women with anxiety, fewer than 8% of the women completed all the web-based CBT and mindfulness-based protocol [84]. Another, large-scale dissemination of Internet-based CBT for youth anxiety found that only 30.31% of participants completed the first three sessions of the program, suggesting that dropout is still a considerable problem in web-based therapy [85]. Another study of 5 fully automated self-help anxiety programs for GAD, SAD, PD/A, OCD, and PTSD found that while 9,394 participants over 18 with one of the above disorders are screened for the program, only 3,880 began a 12-week online mental health program, and only 383 completed posttreatment measures for the program [86]. This study found that completers were more likely to be seeking self-help specifically and have lower scores of nonspecific distress, suggesting that online treatment options may be best as a supplement to in-person treatment for patients who are in less distress and have preferences for online mental health resources [86].

Feasibility of Internet-Mediated Approaches

Various issues impact the feasibility of Internet-mediated approaches including cost, technology burden on providers and patients, and computer literacy. While some research has shown that telehealth can serve as a cost reduction tool for both patients and providers alike [87], many studies have found that there is mixed evidence to support this claim. Two systematic reviews have found that there was limited evidence to support telehealth or telemedicine as a cost-effective approach to healthcare [88, 89];

however, these studies were not limited to psychological interventions, where implementing Internet-mediated interventions have been shown to reduce the cost of treatment [90]. For example, a retrospective cost analysis of a randomized controlled trial investigating telehealth delivery of treatment for anger management for veterans with PTSD showed that telehealth was associated with reduced total staffing and clinic costs compared to in-person delivery [91]. Future research should examine the potential cost-efficacy of telehealth interventions for populations with anxiety.

Providers also face technological burdens in the delivery of Internet-mediated therapies and this is often one of the most cited feasibility issues in various studies [82, 83]. Technological issues are likely to improve as provider literacy increases and the technological aspects of these interventions improve over time. Nonetheless, this is a significant issue that affects provider confidence and convenience. Patients, too, face technological burdens and in some cases discomfort with Internet-mediated approaches [92]. Patients with poor computer literacy may face barriers to the use of digital tools and Internet-mediated interventions [64]. Old age is a factor which has been well established as a barrier to computer literacy [93]; however, promisingly, this may not be true in all cases. One study failed to find any correlation between age and telehealth preferences [73]. Another study of millennials and baby boomers found that baby boomers were more likely to engage in an online intervention to treat depression [92]. More research is needed to understand the technological experience of patients receiving anxiety disorder-specific treatment.

Ambiguous Clinical Practice and Regulatory Guidelines

Providers also face ambiguous or prohibitive regulatory and clinical practice guidelines that affect feasibility of Internet-mediated treatments. In many cases, providers are restricted from practicing across state lines, thereby defeating one of the key purposes of Internet-mediated treatments [94]. Many insurance companies do not adequately, or routinely, reimburse providers for delivering treatment remotely. While some insurance companies pay for Internet-mediated treatments, reimbursement rates are not uniform and may differ depending on the state [36, 95, 96]. Finally, providers face uncertainty with respect to clinical practice guidelines, even when other feasibility concerns are not an issue. For instance, and perhaps most notably, providers lack guidelines about how to adapt these methods when treating more severe clinical conditions, especially when there are patient safety and risk issues. Interestingly, a published case study of an Iraq and Afghanistan veteran who was participating in a clinical trial found that telehealth did not present risk to the patient but, rather, created an opportunity to identify the patient's suicidality and coordinate with the patient, the patient's family, and local resources to develop a safety plan [97]. The Department of Veterans Affairs (VA) has been successfully utilizing telehealth to remotely perform suicide risk assessments; however, complex legal challenges have emerged, including issues of legality regarding involuntary holds and questions regarding liability [98].

As these methods become more ubiquitous, it is almost certain that clinical practice guidelines will become clearer and reimbursement options will improve. Indeed, there is evidence that this is already occurring [96]. In the meantime, researchers are encouraged to study the feasibility, acceptability, and effectiveness of Internet-mediated treatments with more severely anxious and higher-risk populations to inform evidence-based treatment and practice guidelines.

Disparities in Internet-Mediated Interventions

Notably, many mental health apps and research studies regarding the efficacy of web-based interventions for psychopathology have disproportionately targeted white people [71, 76, 99]. This is problematic given that people of color with anxiety disorders report more barriers to care than their nonwhite counterparts [7]. Given the increased barriers to care endorsed by people of color with anxiety disorders [7, 100], and the increased mental health stigma for these communities [101, 102], telemental health offers the possibility of a unique opportunity to address the needs of nonwhite communities with anxiety disorders. While nonwhite communities tend to have less reliable broadband Internet [103], research has demonstrated that communities of color and resource-restricted communities are reliant on smartphones for Internet use as they are less likely than their white counterparts to own computers [104]. It is possible that app-based interventions might be more accessible for these communities. As such, concerted research and clinical and technological efforts should be made to adapt both Internet-mediated and in-person interventions to smartphone devices.

Furthermore, Internet access is not equal. People from lower socioeconomic backgrounds and nonwhite people are less likely to have regular broadband Internet access as well as technological devices (e.g., desktop computers, web cameras) required to access the Internet and are more reliant on smartphones for routine Internet access [103]. Ironically, telehealth, which has been touted as a barrier reduction tool for rural areas, may not be as effective as desired as people in rural areas are less likely to have reliable Internet service [105]. Issues of access are not solely addressed by the development of Internet-mediated interventions; these technological advancements must occur alongside systems and policy developments that increase access to Internet service for at-risk communities including ethnic minorities and individuals in rural areas.

Conclusions

Digital innovations may offer opportunities in the treatment of anxiety disorders, as preventative, supplemental, or even primary treatment options [106]. Internet-mediated approaches to mental healthcare for those with anxiety disorders are via-

ble and effective options; however, more randomized controlled trials with larger and more well-characterized samples of individuals with clinically diagnosed anxiety disorders are needed. Clinicians should consider utilizing these treatment options but should consider any potential barriers to these technologies that hinder optimal access and utilization. Technology is rapidly evolving; mental health treaters and researchers should be informed of these advancements to prevent proliferation of non-evidence-based interventions while advocating for larger systems and policy developments that encourage equal access to Internet-mediated treatments.

References

1. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen H-U. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res. 2012;21:169–84.
2. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:629–40.
3. Young AS, Klap R, Sherbourne CD, Wells KB. The quality of care for depressive and anxiety disorders in the United States. Arch Gen Psychiatry. 2001;58:55–61.
4. Essau CA. Frequency and patterns of mental health services utilization among adolescents with anxiety and depressive disorders. Depress Anxiety. 2005;22:130–7.
5. Chartier-Otis M, Perreault M, Bélanger C. Determinants of barriers to treatment for anxiety disorders. Psychiatry Q. 2010;81:127–38.
6. Coles ME, Coleman SL. Barriers to treatment seeking for anxiety disorders: initial data on the role of mental health literacy. Depress Anxiety. 2010;27:63–71.
7. Goetter EM, Frumkin MR, Palitz SA, Swee MB, Baker AW, Bui E, Simon NM. Barriers to mental health treatment among individuals with social anxiety disorder and generalized anxiety disorder. Psychol Serv. 2018; https://doi.org/10.1037/ser0000254.
8. Lambert JD, Greaves CJ, Farrand P, Price L, Haase AM, Taylor AH. Web-based intervention using behavioral activation and physical activity for adults with depression (the eMotion study): pilot randomized controlled trial. J Med Internet Res. 2018;20:e10112.
9. Fletcher K, Foley F, Thomas N, et al. Web-based intervention to improve quality of life in late stage bipolar disorder (ORBIT): randomised controlled trial protocol. BMC Psychiatry. 2018;18:221.
10. Bell IH, Fielding-Smith SF, Hayward M, Rossell SL, Lim MH, Farhall J, Thomas N. Smartphone-based ecological momentary assessment and intervention in a blended coping-focused therapy for distressing voices: development and case illustration. Internet Interv. 2018;14:18–25.
11. Bucci S, Barrowclough C, Ainsworth J, Machin M, Morris R, Berry K, Emsley R, Lewis S, Edge D, Buchan I. Actissist: proof-of-concept trial of a theory-driven digital intervention for psychosis. Schizophr Bull. 2018;44(5):1070–80. https://doi.org/10.1093/schbul/sby032.
12. Garcia-Palacios A, Botella C, Hoffman H, Fabregat S. Comparing acceptance and refusal rates of virtual reality exposure vs. in vivo exposure by patients with specific phobias. Cyberpsychol Behav. 2007;10:722–4.
13. Wallin E, Maathz P, Parling T, Hursti T. Self-stigma and the intention to seek psychological help online compared to face-to-face. J Clin Psychol. 2018;74:1207–18.
14. Darkins AW, Cary MA. Telemedicine and telehealth: principles, policies, performances and pitfalls. New York: Springer; 2000.

15. Gros DF, Morland LA, Greene CJ, Acierno R, Strachan M, Egede LE, Tuerk PW, Myrick H, Frueh BC. Delivery of evidence-based psychotherapy via video telehealth. J Psychopathol Behav Assess. 2013;35:506–21.

16. Lovell K, Fullalove L, Garvey R, Brooker C. Telephone treatment of obsessive-compulsive disorder. Behav Cogn Psychother. 2000;28:87–91.

17. Krijn M, Emmelkamp PMG, Olafsson RP, Biemond R. Virtual reality exposure therapy of anxiety disorders: a review. Clin Psychol Rev. 2004;24:259–81.

18. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. PLoS ONE. 2010;5:e13196. https://doi.org/10.1371/journal.pone.0013196.

19. Firth J, Torous J, Carney R, Newby J, Cosco TD, Christensen H, Sarris J. Digital Technologies in the Treatment of anxiety: recent innovations and future directions. Curr Psychiatry Rep. 2018;20:44.

20. Titov N, Dear BF, Staples LG, et al. MindSpot clinic: an accessible, efficient, and effective online treatment service for anxiety and depression. Psychiatr Serv. 2015;66:1043–50.

21. Klein B, Meyer D, Austin DW, Kyrios M. Anxiety online—a virtual clinic: preliminary outcomes following completion of five fully automated treatment programs for anxiety disorders and symptoms. J Med Internet Res. 2011;13:e89. https://doi.org/10.2196/jmir.1918.

22. Kaltenthaler E, Sutcliffe P, Parry G, Beverley C, Rees A, Ferriter M. The acceptability to patients of computerized cognitive behaviour therapy for depression: a systematic review. Psychol Med. 2008;38:1521–30.

23. Davies EB, Morriss R, Glazebrook C. Computer-delivered and web-based interventions to improve depression, anxiety, and psychological well-being of university students: a systematic review and meta-analysis. J Med Internet Res. 2014;16:e130.

24. Mathiasen K, Riper H, Andersen TE, Roessler KK. Guided internet-based cognitive behavioral therapy for adult depression and anxiety in routine secondary care: observational study. J Med Internet Res. 2018;20:e10927.

25. Carlbring P, Maurin L, Törngren C, Linna E, Eriksson T, Sparthan E, Strååt M, Marquez von Hage C, Bergman-Nordgren L, Andersson G. Individually-tailored, internet-based treatment for anxiety disorders: a randomized controlled trial. Behav Res Ther. 2011;49:18–24.

26. Titov N, Andrews G, Schwencke G, Robinson E, Peters L, Spence J. Randomized controlled trial of internet cognitive Behavioural treatment for social phobia with and without motivational enhancement strategies. Aust N Z J Psychiatry. 2010;44:938–45.

27. Hoffmann D, Rask CU, Hedman-Lagerlöf E, Ljótsson B, Frostholm L. Development and feasibility testing of internet-delivered acceptance and commitment therapy for severe health anxiety: pilot study. JMIR Ment Health. 2018;5:e28.

28. Viskovich S, Pakenham KI. Pilot evaluation of a web-based acceptance and commitment therapy program to promote mental health skills in university students. J Clin Psychol. 2018;74:2047. https://doi.org/10.1002/jclp.22656.

29. Boettcher J, Åström V, Påhlsson D, Schenström O, Andersson G, Carlbring P. Internet-based mindfulness treatment for anxiety disorders: a randomized controlled trial. Behav Ther. 2014;45:241–53.

30. Benton SA, Heesacker M, Snowden SJ, Lee G. Therapist-assisted, online (TAO) intervention for anxiety in college students: TAO outperformed treatment as usual. Prof Psychol Res Pract. 2016;47:363–71.

31. Tulbure BT, Rusu A, Sava FA, Sălăgean N, Farchione TJ. A web-based transdiagnostic intervention for affective and mood disorders: randomized controlled trial. JMIR Ment Health. 2018;5:e36.

32. Dear BF, Titov N, Schwencke G, Andrews G, Johnston L, Craske MG, McEvoy P. An open trial of a brief transdiagnostic internet treatment for anxiety and depression. Behav Res Ther. 2011;49:830–7.

33. Spence SH, Donovan CL, March S, Kenardy JA, Hearn CS. Generic versus disorder specific cognitive behavior therapy for social anxiety disorder in youth: a randomized controlled trial using internet delivery. Behav Res Ther. 2017;90:41–57.

34. Berger T, Urech A, Krieger T, Stolz T, Schulz A, Vincent A, Moser CT, Moritz S, Meyer B. Effects of a transdiagnostic unguided internet intervention ('velibra') for anxiety disorders in primary care: results of a randomized controlled trial. Psychol Med Camb. 2017;47:67–80.

35. Durland L, Interian A, Pretzer-Aboff I, Dobkin RD. Effect of telehealth-to-home interventions on quality of life for individuals with depressive and anxiety disorders. Smart Homecare Technol TeleHealth. 2014;2:105–19.

36. Whitten P, Buis L. Private payer reimbursement for telemedicine services in the United States. Telemed J E Health. 2007;13:15–24.

37. Bouchard S, Payeur R, Rivard V, Allard M, Paquin B, Renaud P, Goyer L. Cognitive behavior therapy for panic disorder with agoraphobia in videoconference: preliminary results. Cyberpsychol Behav. 2000;3:999–1007.

38. Bouchard S, Paquin B, Payeur R, Allard M, Rivard V, Fournier T, Renaud P, Lapierre J. Delivering cognitive-behavior therapy for panic disorder with agoraphobia in videoconference. Telemed J E Health. 2004;10:13–25.

39. Yuen EK, Herbert JD, Forman EM, Goetter EM, Juarascio AS, Rabin S, Goodwin C, Bouchard S. Acceptance based behavior therapy for social anxiety disorder through videoconferencing. J Anxiety Disord. 2013;27:389–97.

40. Yuen E, Goetter EM, Stasio M, Mansour B, Forte S, Zulaica K, Watkins J. A pilot of acceptance and commitment therapy for public speaking anxiety delivered with group videoconferencing and virtual reality exposure. J Contextual Behav Sci. 2019;12:47–54.

41. Himle JA, Fischer DJ, Muroff JR, Van Etten ML, Lokers LM, Abelson JL, Hanna GL. Videoconferencing-based cognitive-behavioral therapy for obsessive-compulsive disorder. Behav Res Ther. 2006;44:1821–9.

42. Vogel PA, Launes G, Moen EM, Solem S, Hansen B, Håland AT, Himle JA. Videoconference- and cell phone-based cognitive-behavioral therapy of obsessive-compulsive disorder: a case series. J Anxiety Disord. 2012;26:158–64.

43. Himle MB, Freitag M, Walther M, Franklin SA, Ely L, Woods DW. A randomized pilot trial comparing videoconference versus face-to-face delivery of behavior therapy for childhood tic disorders. Behav Res Ther. 2012;50:565–70.

44. Tuerk PW, Fortney J, Bosworth HB, Wakefield B, Ruggiero KJ, Acierno R, Frueh BC. Toward the development of national telehealth services: the role of veterans health administration and future directions for research. Telemed J E-Health. 2009;16:115–7.

45. Shore P, Goranson A, Ward MF, Lu MW. Meeting veterans where they're @: a VA Home-Based Telemental Health (HBTMH) pilot program. Int J Psychiatry Med. 2014;48:5–17.

46. Tuerk PW, Yoder M, Ruggiero KJ, Gros DF, Acierno R. A pilot study of prolonged exposure therapy for posttraumatic stress disorder delivered via telehealth technology. J Trauma Stress. 2010;23:116–23.

47. Bolton AJ, Dorstyn DS. Telepsychology for Posttraumatic Stress Disorder: A systematic review. J Telemed Telecare. 2015;21:254–67.

48. Morland LA, Mackintosh M-A, Greene CJ, Rosen CS, Chard KM, Resick P, Frueh BC. Cognitive processing therapy for posttraumatic stress disorder delivered to rural veterans via telemental health: a randomized noninferiority clinical trial. J Clin Psychiatry. 2014;75:470–6.

49. Rothbaum BO, Hodges LF, Kooper R, Opdyke D, Williford JS, North M. Effectiveness of computer-generated (virtual reality) graded exposure in the treatment of acrophobia. Am J Psychiatry. 1995;152:626–8.

50. Emmelkamp PMG, Bruynzeel M, Drost L, van der Mast CAPG. Virtual reality treatment in acrophobia: a comparison with exposure in vivo. Cyberpsychol Behav. 2001;4:335–9.

51. Morina N, Ijntema H, Meyerbröker K, Emmelkamp PMG. Can virtual reality exposure therapy gains be generalized to real-life? A meta-analysis of studies applying behavioral assessments. Behav Res Ther. 2015;74:18–24.

52. Anderson PL, Zimand E, Hodges LF, Rothbaum BO. Cognitive behavioral therapy for public-speaking anxiety using virtual reality for exposure. Depress Anxiety. 2005;22:156–8.

53. Gonçalves R, Pedrozo AL, Coutinho ESF, Figueira I, Ventura P. Efficacy of virtual reality exposure therapy in the treatment of PTSD: a systematic review. PLoS One. 2012;7: e48469.

54. Rothbaum BO, Anderson P, Zimand E, Hodges L, Lang D, Wilson J. Virtual reality exposure therapy and standard (in vivo) exposure therapy in the treatment of fear of flying. Behav Ther. 2006;37:80–90.

55. Bouchard S, Dumoulin S, Robillard G, Guitard T, Klinger É, Forget H, Loranger C, Roucaut FX. Virtual reality compared with in vivo exposure in the treatment of social anxiety disorder: a three-arm randomised controlled trial. Br J Psychiatry. 2017;210:276–83.

56. Kramer TL, Pyne JM, Kimbrell TA, Savary PE, Smith JL, Jegley SM. Clinician perceptions of virtual reality to assess and treat returning veterans. Psychiatr Serv. 2010;61:1153–6.

57. Segal R, Bhatia M, Drapeau M. Therapists' perception of benefits and costs of using virtual reality treatments. Cyberpsychol Behav Soc Netw. 2011;14:29–34.

58. McCann RA, Armstrong CM, Skopp NA, Edwards-Stewart A, Smolenski DJ, June JD, Metzger-Abamukong M, Reger GM. Virtual reality exposure therapy for the treatment of anxiety disorders: an evaluation of research quality. J Anxiety Disord. 2014;28:625–31.

59. Page S, Coxon M. Virtual reality exposure therapy for anxiety disorders: small samples and no controls? Front Psychol. 2016;7 https://doi.org/10.3389/fpsyg.2016.00326.

60. Kamkuimo Kengne SA, Fossaert M, Girard B, Menelas B-AJ. Action-centered exposure therapy (ACET): a new approach to the use of virtual reality to the Care of People with posttraumatic stress disorder. Behav Sci. 2018;8:76.

61. Matthews AJ, Maunder R, Scanlan JD, Kirkby KC. Online computer-aided vicarious exposure for OCD symptoms: a pilot study. J Behav Ther Exp Psychiatry. 2017;54:25–34.

62. Yuen EK, Herbert JD, Forman EM, Goetter EM, Comer R, Bradley J-C. Treatment of social anxiety disorder using online virtual environments in second life. Behav Ther. 2013;44:51–61.

63. Pramana G, Parmanto B, Lomas J, Lindhiem O, Kendall PC, Silk J. Using mobile health gamification to facilitate cognitive behavioral therapy skills practice in child anxiety treatment: open clinical trial. JMIR Serious Games. 2018;6:e9.

64. Price M, Yuen EK, Goetter EM, Herbert JD, Forman EM, Acierno R, Ruggiero KJ. mHealth: a mechanism to deliver more accessible, more effective mental health care. Clin Psychol Psychother. 2014;21:427–36.

65. Stolz T, Schulz A, Krieger T, Vincent A, Urech A, Moser C, Westermann S, Berger T. A mobile app for social anxiety disorder: a three-arm randomized controlled trial comparing mobile and PC-based guided self-help interventions. J Consult Clin Psychol. 2018;86:493–504.

66. Weisel KK, Zarski A-C, Berger T, Schaub MP, Krieger T, Moser CT, Berking M, Ebert DD. Transdiagnostic tailored internet- and Mobile-based guided treatment for major depressive disorder and comorbid anxiety: study protocol of a randomized controlled trial. Front Psych. 2018;9:274.

67. Bui E, Blackburn AM, Brenner LH, Laifer LM, Park ER, Fricchione GL, Sylvia LG. Military and veteran caregivers' perspectives of stressors and a mind-body program. Issues Ment Health Nurs. 2018;39:850–7.

68. Harrer M, Adam SH, Fleischmann RJ, et al. Effectiveness of an internet- and app-based intervention for college students with elevated stress: randomized controlled trial. J Med Internet Res. 2018;20:e136.

69. Economides M, Martman J, Bell MJ, Sanderson B. Improvements in stress, affect, and irritability following brief use of a mindfulness-based smartphone app: a randomized controlled trial. Mindfulness. 2018;9:1584–93.

70. Cox CE, Hough CL, Jones DM, et al. Effects of mindfulness training programmes delivered by a self-directed mobile app and by telephone compared with an education programme for survivors of critical illness: a pilot randomised clinical trial. Thorax. 2018;74:33. https://doi.org/10.1136/thoraxjnl-2017-211264.

71. Parker L, Bero L, Gillies D, Raven M, Mintzes B, Jureidini J, Grundy Q. Mental health messages in prominent mental health apps. Ann Fam Med. 2018;16:338–42.
72. Hadjistavropoulos HD, Faller YN, Klatt A, Nugent MN, Dear BF, Titov N. Patient perspectives on strengths and challenges of therapist-assisted internet-delivered cognitive behaviour therapy: using the patient voice to improve care. Community Ment Health J. 2018;54:944. https://doi.org/10.1007/s10597-018-0286-0.
73. Goetter EM, Blackburn AM, Bui E, Laifer LM, Simon NM. Veterans' prospective attitudes about mental health treatment using telehealth. J Psychosoc Nurs Ment Health Serv. 2019;59(9):38–43.
74. Musiat P, Goldstone P, Tarrier N. Understanding the acceptability of e-mental health – attitudes and expectations towards computerised self-help treatments for mental health problems. BMC Psychiatry. 2014;14:109.
75. Fleischmann RJ, Harrer M, Zarski A-C, Baumeister H, Lehr D, Ebert DD. Patients' experiences in a guided internet- and app-based stress intervention for college students: a qualitative study. Internet Interv. 2018;12:130–40.
76. Knowles SE, Toms G, Sanders C, et al. Qualitative meta-synthesis of user experience of computerised therapy for depression and anxiety. PLoS One. 2014;9 https://doi.org/10.1371/journal.pone.0084323.
77. Apolinário-Hagen J, Fritsche L, Bierhals C, Salewski C. Improving attitudes toward e-mental health services in the general population via psychoeducational information material: a randomized controlled trial. Internet Interv. 2018;12:141–9.
78. Perle JG, Langsam LC, Randel A, Lutchman S, Levine AB, Odland AP, Nierenberg B, Marker CD. Attitudes toward psychological telehealth: current and future clinical psychologists' opinions of internet-based interventions. J Clin Psychol. 2013;69:100–13.
79. Chavira DA, Bustos CE, Garcia MS, Ng B, Camacho A. Delivering CBT to rural Latino children with anxiety disorders: a qualitative study. Community Ment Health J. 2017;53:53–61.
80. Pihlaja S, Stenberg J-H, Joutsenniemi K, Mehik H, Ritola V, Joffe G. Therapeutic alliance in guided internet therapy programs for depression and anxiety disorders – a systematic review. Internet Interv. 2018;11:1–10.
81. Geramita EM, Herbeck Belnap B, Abebe KZ, Rothenberger SD, Rotondi AJ, Rollman BL. The association between increased levels of patient engagement with an internet support group and improved mental health outcomes at 6-month follow-up: post-hoc analyses from a randomized controlled trial. J Med Internet Res. 2018;20:e10402.
82. Goetter EM, Herbert JD, Forman EM, Yuen EK, Gershkovich M, Glassman LH, Rabin SJ, Goldstein SP. Delivering exposure and ritual prevention for obsessive–compulsive disorder via videoconference: clinical considerations and recommendations. J Obsessive Compuls Relat Disord. 2013;2:137–45.
83. Yuen EK, Goetter EM, Herbert JD, Forman EM. Challenges and opportunities in internet-mediated telemental health. Prof Psychol Res Pract. 2012;43:1–8.
84. Ashford MT, Olander EK, Rowe H, Fisher JR, Ayers S. Feasibility and acceptability of a web-based treatment with telephone support for postpartum women with anxiety: randomized controlled trial. JMIR Ment Health. 2018;5:e19.
85. March S, Spence SH, Donovan CL, Kenardy JA. Large-scale dissemination of internet-based cognitive behavioral therapy for youth anxiety: feasibility and acceptability study. J Med Internet Res. 2018;20:e234.
86. AM AL-A, Klein B, Meyer D. Posttreatment attrition and its predictors, attrition Bias, and treatment efficacy of the anxiety online programs. J Med Internet Res. 2014;16 https://doi.org/10.2196/jmir.3513.
87. de la Torre-Díez I, López-Coronado M, Vaca C, Aguado JS, de Castro C. Cost-utility and cost-effectiveness studies of telemedicine, electronic, and Mobile health systems in the literature: a systematic review. Telemed J E Health. 2014;21:81–5.
88. Mistry H. Systematic review of studies of the cost-effectiveness of telemedicine and telecare. Changes in the economic evidence over twenty years. J Telemed Telecare. 2012;18:1–6.

89. Whitten PS, Mair FS, Haycox A, May CR, Williams TL, Hellmich S. Systematic review of cost effectiveness studies of telemedicine interventions. BMJ. 2002;324:1434–7.
90. Crow SJ, Mitchell JE, Crosby RD, Swanson SA, Wonderlich S, Lancanster K. The cost effectiveness of cognitive behavioral therapy for bulimia nervosa delivered via telemedicine versus face-to-face. Behav Res Ther. 2009;47:451–3.
91. Morland LA, Raab M, Mackintosh M-A, Rosen CS, Dismuke CE, Greene CJ, Frueh BC. Telemedicine: a cost-reducing means of delivering psychotherapy to rural combat veterans with PTSD. Telemed J E Health. 2013;19:754–9.
92. Schneider BC, Schröder J, Berger T, et al. Bridging the "digital divide": a comparison of use and effectiveness of an online intervention for depression between baby boomers and millennials. J Affect Disord. 2018;236:243–51.
93. Vaportzis E, Giatsi Clausen M, Gow AJ. Older adults perceptions of technology and barriers to interacting with tablet computers: a focus group study. Front Psychol. 2017;8 https://doi.org/10.3389/fpsyg.2017.01687.
94. Herbert JD, Goetter EM, Forman EM, Yuen EK, Erford BM, Milillo JJ, Goldstein SP. Crossing the line: interstate delivery of remote psychological services. Behav Ther. 2012;35:145–52.
95. George BP, Scoglio NJ, Reminick JI, Rajan B, Beck CA, Seidmann A, Biglan KM, Dorsey ER. Telemedicine in leading US neurology departments. Neurohospitalist. 2012;2:123–8.
96. Mehrotra A, Jena AB, Busch AB, Souza J, Uscher-Pines L, Landon BE. Utilization of telemedicine among rural Medicare beneficiaries. JAMA. 2016;315:2015–6.
97. Gros DF, Veronee K, Strachan M, Ruggiero KJ, Acierno R. Managing suicidality in home-based telehealth. J Telemed Telecare. 2011;17:332–5.
98. Godleski L, Nieves JE, Darkins A, Lehmann L. VA telemental health: suicide assessment. Behav Sci Law. 2008;26:271–86.
99. Dorstyn DS, Saniotis A, Sobhanian F. A systematic review of telecounselling and its effectiveness in managing depression amongst minority ethnic communities. J Telemed Telecare. 2013;19:338–46.
100. Williams MT, Domanico J, Marques L, Leblanc NJ, Turkheimer E. Barriers to treatment among African Americans with obsessive-compulsive disorder. J Anxiety Disord. 2012;26:555–63.
101. Memon A, Taylor K, Mohebati LM, Sundin J, Cooper M, Scanlon T, de Visser R. Perceived barriers to accessing mental health services among black and minority ethnic (BME) communities: a qualitative study in Southeast England. BMJ Open. 2016;6:e012337.
102. Gary FA. Stigma: barrier to mental health care among ethnic minorities. Issues Ment Health Nurs. 2005;26:979–99.
103. Pew Research Center. Demographics of internet and home broadband usage in the United States; 2018. https://www.pewinternet.org/fact-sheet/internet-broadband/.
104. Pew Research Center. Demographics of mobile device ownership and adoption in the United States. https://www.pewinternet.org/fact-sheet/mobile/.
105. Pew Research Center, Parker K, Horowitz JM, Brown A, Fry R, Cohn D, Igielnik R. Similarities and differences between urban, suburban and rural communities in America; 2018. https://www.pew-socialtrends.org/2018/05/22/what-unites-and-divides-urban-suburban-and-rural-communities/.
106. Hennemann S, Farnsteiner S, Sander L. Internet- and mobile-based aftercare and relapse prevention in mental disorders: a systematic review and recommendations for future research. Internet Interv. 2018;14:1–17.

Chapter 17
Understanding and Treating Anxiety Disorders: A Psychodynamic Approach

Jonah N. Cohen and Simona C. Kaplan

This chapter outlines psychodynamic conceptualizations and treatments of anxiety disorders (social anxiety, generalized anxiety, panic and agoraphobia, and specific phobia) from Freud to the current day. Specifically, we trace psychodynamic theory from a one-person psychology to a two-person model.[1] We then describe contemporary psychodynamic theories of anxiety disorders. Next, we review and critically evaluate the empirical support for psychodynamic psychotherapies for anxiety disorders. We conclude by suggesting empirical and theoretical future directions for the psychodynamic treatment of anxiety disorders.

Overview of Psychodynamic Theory

Psychodynamic theory posits the existence of an unconscious mind, a core concept that differentiates it from other therapeutic orientations. According to psychodynamic theory, unconscious drives, wishes, and motivations influenced by early childhood experiences come into conflict with their conscious counterparts. Individuals, in an effort to find a compromise between their unconscious and con-

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[1] Given the brevity of this chapter, we will necessarily omit substantial theory and theorists that should otherwise be discussed.

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scious minds, use defense mechanisms (which can be understood as unconscious coping mechanisms) to keep conflict at bay. Psychological symptoms emerge from unconscious conflicts and insufficient defense mechanisms.

In the context of psychodynamic psychotherapy, the "presenting problem" (often symptoms) with which the patient presents is usually not the target of treatment. Instead, the psychodynamic psychotherapist considers the actual problem to be something of which the patient is not yet aware, such as an unconscious conflict. Thus, the goal of treatment is not symptom reduction per se, but rather the uncovering of the origins of the symptom. Symptom alleviation occurs as a consequence of identifying, understanding, and working through unconscious conflict.

Development of Psychodynamic Theory of Anxiety

Anxiety and Freud's Topographic and Structural Hypotheses

The topographical hypothesis was Freud's first attempt at modeling the psyche [1–3]. Freud conjectured that the human psyche comprises the unconscious, the preconscious, and the conscious. He imagined the mind as a seething cauldron of psychic forces pushing to be released. Over time, the excitation of these forces increases, ultimately moving toward discharge (i.e., cathexis). However, instead of being expressed, some psychic material (such as forbidden hate, sexual drives, or aggression) is kept unconscious by repression. The failure to eventually discharge these feelings/urges culminates in anxious symptoms, called neurotic anxiety. Thus, in the topographic theory, anxiety is a result of repression.

Ultimately, however, Freud rejected his original hypothesis and, in its stead, offered the structural hypothesis [4, 5], which marked the beginning of Freud's tripartite model of the mind (i.e., the *id*, *ego*, and *superego*). According to Freud, the *id* is the part of the mind that contains basic drives such as sex and aggression, the *superego* contains the moral conscience, and the *ego* is part that is grounded in reality, responsible for mediating between the *id* and the *superego*. Freud no longer conceptualized the mind as a seething cauldron, but rather understood it as an entity in conflict and compromise. In the structural model, anxiety manifests in the ego. Initially, Freud theorized that conflicts between the *ego* and the *id*, the *ego* and the *superego*, and the *ego* and the external world yield distinct types of anxiety [4].

Freud eventually condensed the different types of anxiety into traumatic anxiety and neurotic anxiety [5]. Traumatic anxiety is automatically triggered in situations of (internal or external) danger that one's *ego* is not equipped to handle. For example, immediately after birth, babies might automatically experience traumatic anxiety because their *ego* is not sufficiently developed to address the strangeness of their new reality. In contrast to traumatic anxiety, neurotic anxiety results from the *ego* feeling threatened by *imagined* dangers that are emblematic of earlier traumatic experiences. For instance, the experience of separation from one's mother in infancy may lead to neurotic anxiety in adulthood in response to the threatened loss of a

friend. In the context of neurotic anxiety, one experiences an affective signal of impending danger (i.e., signal anxiety), after which psychological defenses are engaged in an effort to protect the *ego* from reexperiencing this danger. In other words, in this model, anxiety may be an indication (i.e., signal) of potentially distressing threats to the ego such as shame, trauma, or narcissistic threat. Thus, the structural hypothesis posits that anxiety leads to repression (and other defense mechanisms), whereas in the earlier topographic theory, anxiety is a result of repressed forbidden impulses. Freud's later work expanded into ego psychology, placing a greater emphasis on development, defenses, and the role of the *ego*.

Psychodynamics, Anxiety, and a Two-Person Psychology

In the 1920s, object relations theory developed, shifting the model of the mind from a one-person to a two-person psychology. Object relations theorists believed that in order to understand the human experience, one must consider not only the psychic drives within a single person but also how one's relationships with others shape the psychic experience of the individual (e.g., [6, 7]). Psychoanalysts such as Melanie Klein and Donald Winnicott theorized that anxiety emerged from disrupted attachment and the loss, or threatened loss, of a relationship.

According to Melanie Klein [6–8], infants are born into a state of anxiety, seeking survival in a dangerous world. To cope with this anxiety, infants split good qualities from bad qualities, qualities in others (typically the primary caretaker), and the good qualities in themselves. Because infants locate the "bad" in others and desire to destroy them as a result, infants develop a sense of paranoia about others potentially seeking revenge on them. Thus, according to Klein, infants cope with a world they experience as uncertain and unsafe by dividing the good from the bad, which leads to anxiety. As infants develop, however, they begin to understand people as having both good and bad qualities, forming a more integrated sense of themselves and others. Consequently, the infant's primary caretaker, albeit imperfect, can still be loved. The understanding that people can evoke anger and simultaneously be worthy of love leads the infant to develop a new kind of anxiety, characterized by guilt rather than paranoia. The infant feels guilty for the previous wish to destroy the object.

In sum, according to Klein, the early stages of development are characterized by fears of annihilation, and the later stages are characterized by anxiety about annihilating others. Thus, anxiety takes two forms: the expectation that something bad will happen to oneself and the expectation that something bad will happen to another. Crucially, the anxiety experienced in the context of early relationships is conjectured to repeat throughout the individual's life when confronting similar relational circumstances.

Compared to Klein, Winnicott more greatly emphasized the infant's attachment to the mother early in life [9]. For Winnicott, the bedrock of proper development is attuned caregiving, and anxiety emerges when there is a disruption in a child's attachment to the primary caregiver. Winnicott believed that if infants could safely

express their needs and expect such needs to be met, infants would establish a true (versus false) sense of self. Individuals with a true sense of self are able to have spontaneous and authentic experiences that are not contingent on others. In contrast, those with a false sense of self experience themselves only in relation to the expectations of others. Disrupted attachment sets the stage for numerous problems one encounters later in life, including a threatened sense of interpersonal safety and, subsequently, feelings of anxiety when expressing one's emotions to others.

Following Winnicott's work on a false self, Heinz Kohut launched an investigation into narcissism and ultimately developed a theory termed "self-psychology" [10, 11]. Kohut believed that, in order to establish a sense of self, children need to idealize their primary attachment figure and have that idealization mirrored back. Kohut conjectured that narcissism results from children growing up with poorly attuned parental attachment figures who failed to empathize with and idealize them, leading to anxious feelings of inadequacy that are ultimately defended against by narcissistic tendencies.

In the last several decades, relational (or intersubjective) psychodynamic theory has emerged as a technical extension of object relations theory (e.g., [12]). Relational theory and object relations theory share similar conceptualizations of the origins and nature of psychopathology but differ on the therapist's treatment technique. Relational theory views psychotherapy as a shared process between therapist and patient, where meaning and understanding are co-constructed.

Contemporary Psychodynamic Theories of Anxiety

Common Themes Across Anxiety Disorders

A common feature of many anxiety disorders, per contemporary psychodynamic theory, is the conflict between the wish to be autonomous (separate from others) and the fear of separation (which may result in a strong dependency on others) [13]. Consistent with object relations theory, anxiety disorders are often thought to result from insecure attachments, leading to poorly internalized representations of the self and others that make it hard to feel connected to another person in their physical absence. Thus, anxious individuals often require the presence of another person to experience a sense of security [13].

Panic Disorder

According to the American Psychiatric Association [14], a panic attack is a sudden rush of intense fear or discomfort accompanied by several physical symptoms, and panic disorder (PD) is the presence of panic accompanied by the fear of

having more panic attacks and/or subsequent maladaptive changes in behavior (e.g., avoidance of situations believed to provoke panic). Psychodynamic models of panic [15, 16] emphasize core conflicts related to dependency and anger as significant etiological factors. Individuals with panic are believed to have a genetic vulnerability to anxiety in unfamiliar situations, which leads them, in childhood, to seek safety and comfort from their parents more frequently than their non-anxious counterparts. Inevitably, these children come to experience their parents as failing to gratify all their dependent wishes, fostering feelings of anger. These children, however, inhibit the expression of anger due to a fear that it could lead to separation from their parents, which could result in feeling even more unprotected and vulnerable. Conflicts around dependency in PD may also include wishes for independence.

According to psychodynamic models of PD [15, 16], these childhood conflicts (i.e., anger vs. fear of retaliation; dependency vs. autonomy) are repeated in the context of adult relationships; they may evoke panic symptoms when an individual experiences a threat to a current significant relationship. For example, individuals with panic are thought to react with anger when facing threats of separation or entrapment but simultaneously do not allow themselves to experience anger, as its expression could lead to the realization of their feared scenario. Thus, panic symptoms are understood as somatic manifestations of an unconscious emotion (typically anger). Importantly, by having a panic attack, individuals may provoke attention from others, potentially gratifying the original dependency wish.

Social Anxiety Disorder

Social anxiety disorder (SAD) is a chronic and impairing disorder characterized by fear of negative evaluation and/or humiliation, resulting in avoidance of feared social interaction or performance situations [14]. Psychodynamic theory of SAD [17] posits that the condition results from unresolved conflicts involving a wish, the response to the wish that one anticipates from other people, and a subsequent response from the self, which manifests as the patient's symptoms. This wish-response triad comprises the "Core Conflictual Relationship Theme" (CCRT; [18]). Though the specific content of the CCRT varies from individual to individual, a typical person with social anxiety may have a core conflict related to closeness, with a CCRT which includes the wish "I want to be accepted by others," the response "others might reject or humiliate me," and the response from the self (i.e., the SAD symptoms such as avoidance) of trying to control the impression one makes on others and avoiding self-exposure or vulnerability. The CCRT in a socially anxious person is triggered by the perception of interpersonal threat. The activation of the CCRT brings about feelings of fear, loss of control, helplessness, and hopelessness—psychological experiences that are often accompanied by physiological anxiety symptoms.

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive anxiety and worry, accompanied by physical symptoms [14]. Contemporary psychodynamic theory posits that chronic worry may result from early relationships that predispose the individual to experience relationships as fragile [19]. Specifically, the understanding of relationships as fragile could stem from insecure attachment to primary caregivers, including feeling uncertain about whether one can depend on the parent in times of need, the perception that one may be rejected by the parent, or the experience of role reversal in which the child needs to care for an incompetent parent [20]. Insecure attachments to early caregivers may lead to a conflict between the wish for dependency and the need to become autonomous. Such insecure attachments can also contribute to the conflict between desire for closeness to attachment figures and fears of enmeshment or identity loss.

Busch and Milrod [21] suggest that, taken together, worry arises from efforts to maintain control (either actively or passively via avoidance) within relationships in order to prevent disrupted attachments. For instance, unconscious hostile or angry feelings can trigger anxiety and the fear of being rejected for such emotions, leading patients to inhibit their anger [21] and instead worry about various more superficial events or activities in their life. Worry is thus conceptualized as a defense mechanism that protects the anxious individual from thinking about difficult feelings or distressing issues [20, 22], such as feelings of loss of control or separations from loved ones. Worry and concomitant physical anxiety symptoms are activated to keep more threatening thoughts, feelings, or memories out of awareness [22].

Agoraphobia

Agoraphobia is characterized by anxiety about being in situations in which escape would be difficult and/or help is not readily available [14]. To date, no empirically established psychodynamic model of agoraphobia exists. Generally, agoraphobia, like panic, is believed to be an unconscious way of controlling the closeness of significant attachment relationships. For instance, individuals may avoid leaving a familiar environment in order to remain both physically and emotionally close to an attachment figure that they fear losing. The psychodynamic treatment of agoraphobia tends to focus on elucidating the connection between the patients' current dependence on others and their childhood dependency wishes [23, 24].

Specific Phobia

A specific phobia is an intense and irrational fear of an object or situation [14]. To date, there are no empirically based psychodynamic theories of specific phobia. Phobias are believed to be symptomatic expressions of wishes and/or fears that a

patient finds unacceptable and are thus kept unconscious [25]. For example, a specific phobia of flying on an airplane or other modes of travel may represent fears about the tenuousness of attachment relationships, insofar as travel may be unconsciously experienced as threatening an attachment.

Empirical Support for Psychodynamic Psychotherapy for Anxiety Disorders

Research Across Anxiety Disorders

The major goals of psychodynamic psychotherapy are to uncover unconscious core conflicts, to work through them, and to modify one's maladaptive defense mechanisms, finding more adaptive ways to respond. Recently, some psychodynamically informed researchers and clinicians have made efforts to create manualized protocols to guide psychodynamic psychotherapy, both for specific disorders and for transdiagnostic emotional difficulties [26].

Generally, the extant empirical literature suggests that psychodynamic psychotherapies for a wide range of psychological disorders, including anxiety disorders, yield large effect sizes comparable to other psychotherapies that have been deemed "empirically supported" and "evidence based." Furthermore, the "active ingredients" of other evidence-based treatments are elements that have been core to psychodynamic therapy since its origination (e.g., the establishment of a quality working alliance; [27]).

In a meta-analysis examining the efficacy of treatments for anxiety disorders [28], including GAD, PD with and without agoraphobia, and SAD, the average pre-post effect size for psychodynamic therapy was 1.17 ($n = 5$), compared to 1.56 ($n = 4$) for mindfulness therapies, 1.30 for individual cognitive-behavioral/exposure therapy ($n = 93$), and 0.83 for psychological placebos ($n = 16$). The authors did not test for significant differences in efficacies of theoretically divergent psychotherapies, though interpretation of the confidence intervals suggests that they are not significantly different. In another meta-analysis of 14 randomized controlled trials (RCTs) examining the controlled effects of psychodynamic psychotherapy for anxiety disorders [29], psychodynamic psychotherapy was significantly more effective than controls and was found to be as efficacious as active psychotherapies [e.g., cognitive-behavioral therapy (CBT)] at posttreatment and follow-up time points.

Panic Disorder with or Without Agoraphobia

Contemporary and manualized treatment protocols for PD [16, 17] are time limited and focused. The treatment has three main phases: (1) treatment of acute panic, (2) treatment of panic vulnerability, and (3) consolidation of gains and termination. In

the first phase of psychodynamic treatment, the therapist works with patients to elucidate the meaning and function of their panic symptoms, aiming to attenuate panic through this awareness. Phase II uses the therapeutic relationship/transference to treat patients' overall vulnerability to panic. In this phase, the therapist works to address patients' conflicts between dependency and anger in their relationship with the therapist. In the final phase, the termination of treatment is utilized to extend gains by encouraging patients to directly address difficulties with separation and independence in the context of therapy's termination.

Milrod and colleagues [30] conducted a pilot open trial of a manualized panic-focused psychodynamic psychotherapy (PFPP; [31]). Twenty-one patients with Diagnostic and Statistical Manual (DSM)-IV PD with or without agoraphobia received 24 sessions of twice-weekly PFPP. Sixteen of these patients achieved remission of panic and agoraphobia, and for those who began treatment with comorbid depression, their depression remitted. Gains were maintained at 6-month follow-up. Milrod and colleagues [32] next conducted a randomized controlled trial of 12 weeks of twice-weekly PFPP or applied relaxation training (ART) for PD. Patients were 49 adults with DSM-IV PD. Significantly more patients in PFPP (73%) than ART (39%) responded to treatment, and patients receiving PFPP demonstrated significantly greater reductions in functional impairment. This study indicated preliminary efficacy of PFPP.

In a larger, two-site [Weill Cornell Medical College (Cornell) and University of Pennsylvania (Penn)] RCT, Milrod and colleagues [33] randomized 201 patients with DSM-IV PD with and without agoraphobia to receive 19–24 sessions over 12 weeks of CBT, PFPP, or ART. There was a site by treatment interaction; response rates at Cornell significantly differed across treatments, such that CBT and PFPP were superior to ART. However, there were no significant differences in response rates between any of the three conditions at Penn. At Penn, patients in ART and CBT improved significantly faster and demonstrated greater panic symptom reduction than those in PFPP, whereas there were no such differences across groups at Cornell. All treatments yielded significant improvements in panic symptoms, but patients considered ART less acceptable. Notably, both CBT and psychodynamic psychotherapy had strong allegiance at both sites, but Cornell had more experience with the PFPP protocol. Additionally, psychodynamic supervision was conducted more frequently over the phone (rather than in person) at Penn compared to Cornell. This study suggests that, despite the effectiveness of this particular psychodynamic psychotherapy protocol, outcomes may be influenced by levels of experience and quality of supervision received at a given site. At Cornell, there were no differences between CBT and PFPP in terms of response rates, symptom improvement, or speed of improvement.

Social Anxiety Disorder

Leichsenring and colleagues [17] created a psychodynamic treatment manual for SAD based on Luborsky's [18] supportive-expressive psychotherapy. In the early phase of this treatment, the therapist works to establish goals and a therapeutic alli-

ance, identifies the CCRT through observing patterns in patients' descriptions of interpersonal interactions or relationships in their life, and discusses the connection between the CCRT and the patient's symptoms. The next phase of treatment involves exploring the ways in which the CCRT influences patients' current relationships, including the therapist-patient relationship. The patients' social avoidance (i.e., the response from the self or the symptom) is conceptualized as a defense mechanism that leads to the self-fulfillment of feared outcomes, such as negative evaluation from others or social isolation. Thus, the therapist encourages patients to respond differently to their internal conflict, instructing patients to engage in self-exposure to feared situations outside of the therapy room. In the last phase, the therapist works with patients to synthesize what has been learned and discuss how the CCRT might manifest in symptom resurgence during the process of termination due to the anticipated loss of the therapist. Booster sessions may be used to monitor and support continued progress, encourage self-guided exposure, and connect relapse with the CCRT [18].

In a multicenter controlled noninferiority trial, Leichsenring et al. [34] randomly assigned adults with DSM-IV [35] SAD to receive up to 25 sessions of CBT ([36]; $n = 209$), psychodynamic psychotherapy ($n = 207$), or a wait-list control (WL; $n = 79$). Though significantly more patients achieved remission in CBT (36%) than in psychodynamic psychotherapy (26%), the treatments did not yield significantly different response rates (60% in CBT vs. 52% in psychodynamic). Both active treatments demonstrated superior response and remission rates compared to WL. CBT patients showed significantly greater improvement than psychodynamic patients on measures of social anxiety (SA) and interpersonal problems, but not depression. However, at 6-month follow-up, there were no differences in response or remission rates between treatments. At a 2-year follow-up [37], no differences existed between the treatments as both had response rates of about 70% and remission rates of about 40%. In sum, there were small effects suggesting the superiority of CBT on some, but not every symptom measure at posttreatment, but the efficacy of the two treatments was not different at follow-up.

In another randomized trial [38], patients with SAD ($N = 47$) received up to 36 sessions of psychodynamic psychotherapy or CBT. Both treatments exhibited large within-subject effect sizes. There were no significant differences between the two treatments at posttreatment or follow-up. Sixty-three percent of patients in psychodynamic psychotherapy and 64% of patients in CBT demonstrated clinically significant change in SA [39]. At 1-year follow-up, 75% of patients in psychodynamic psychotherapy, and 65% of patients in CBT, had achieved clinically significant change, corroborating Leichsenring et al.'s [37] finding that neither response nor remission rates differ between the two treatments at follow-up. However, psychodynamic psychotherapy required slightly more sessions than CBT to produce comparable outcomes.

Research also suggests that Internet-based psychodynamic psychotherapy is efficacious for SAD. Johansson et al. [40] conducted an RCT comparing a 10-week Internet-based affect-focused psychodynamic therapy (IPDT; $n = 36$) for SAD to WL ($n = 36$). IPDT involved helping patients conceptualize their difficulties as an "internal affect phobia," identify underlying affects that are more adaptive, gain

insight into defensive behaviors, and work to resolve internal conflicts arising in current interpersonal contexts. IPDT was superior to WL at posttreatment, and this effect was large (Cohen's $d = 1.05$). SA symptom levels continued to decline significantly at 2-year follow-up for the treated group.

Generalized Anxiety Disorder

Treatment for GAD [19, 22] is based on the CCRT and the attachment themes described above. In GAD, a patient's perceptions of current relationships are believed to be distorted because of earlier relational experiences. The CCRT wish in the patient with GAD often involves the wish to be protected or cared for, with the anticipation of a negative response from others, which triggers the patient's response of worry and anxiety. The therapist helps patients identify the CCRT and the links between the patients' relationship patterns, symptoms, and maladaptive methods of coping, while helping patients revise their perceptions of their relationships. During the termination phase, the therapist links the CCRT and the patient's relational fears to the anticipated loss of the therapist. For instance, if worry reemerges during termination, the therapist helps the patient understand the symptom as a means of defending against distress about losing the therapist, which mirrors distress associated with losing an attachment figure.

Crits-Cristoph et al. [19] developed a brief, 16-session supportive-expressive psychotherapy based on Luborsky's CCRT model, adapted specifically for GAD, which focused on understanding anxiety and worry in the context of interpersonal and intrapsychic conflicts. In an open trial [41], the treatment resulted in significant changes on all outcome measures of anxiety, worry, and depression. Ratings of therapist competence and adherence suggested that the manual could be implemented with fidelity and indicated discriminant validity of the treatment (i.e., that it could be differentiated from other treatments). Critz-Christoph et al. [42] followed this open trial with a pilot randomized controlled trial comparing supportive-expressive psychotherapy for adults with DSM-IV GAD ($n = 15$) to supportive therapy ($n = 16$). Remission rates were significantly higher in the supportive-expressive (46%) compared the to the supportive (12.5%) group.

Leichsenring et al. [43] conducted an RCT comparing CBT to short-term psychodynamic psychotherapy, based on Crits-Christoph's [19] supportive-expressive therapy manual. Treatment focused on modifying the patient's CCRT by using the therapeutic alliance to facilitate corrective emotional experiences. Further, the treatment focused on encouraging new behaviors in an effort to modify the CCRT. Patients received up to 30 sessions of CBT ($n = 29$) or psychodynamic psychotherapy ($n = 28$). The mean number of sessions did not differ between the two groups. Patients in both treatments demonstrated significant and large improvements in symptoms of anxiety and depression at posttreatment and 6-month follow-up. The two treatments did not differ at posttreatment or follow-up on the primary outcome measure of anxiety or two corroborating anxiety symptom measures. However, CBT was superior on measures of worry, trait anxiety, and depression. At

6-month follow-up, the two treatments did not differ on most symptom measures; however, CBT yielded superior improvements in trait anxiety and worry. At 12-month follow up [44], both treatments maintained large improvements on the primary outcome measure of anxiety and three corroborating self-report measures, with no differences between groups. After 1 year, CBT was superior to psychodynamic psychotherapy with regard to trait anxiety and worry, but not depression.

In a randomized controlled superiority trial [45], individuals with DSM-IV GAD received Internet-based CBT (ICBT; $n = 27$), Internet-based psychodynamic treatment (IPDT; $n = 27$), or WL ($n = 27$). Each Internet-based treatment included weekly written communication with a therapist related to the specific treatment themes. Both treatments were superior to WL at posttreatment on the primary outcome measure assessing worry, with moderate effect sizes, and did not differ from each other. Both treatments had moderate to large within-group effect sizes at 3- and 18-month follow-ups on the primary measure and did not differ significantly from each other. The two treatments were only marginally better than WL at 3-month follow-up. Overall, the treatments were similarly efficacious on the primary worry measure and on secondary outcome measures of anxiety and depression.

Agoraphobia

To our knowledge, there is only one study examining treatments for patients with PD with (and not without) agoraphobia [46]. Patients with DSM-III-R [47] PD with agoraphobia were hospitalized for 11 weeks and received either an integrative treatment that integrated exposure therapy and psychodynamic group therapy and was developed specifically to target agoraphobia (IT; $n = 37$) or psychodynamic group therapy as usual that was conducted with people with a range of diagnoses (AU; $n = 32$). Fifty-eight percent of patients in IT had significantly improved at posttreatment (as determined by at least 50% improvement on posttreatment relative to pretreatment scores), and 61% had improved at follow-up, compared to 41% and 26% at posttreatment and follow-up, respectively, for those in AU. The proportion of responders was significantly greater for IT than PT at follow-up, but not at posttreatment. Though interesting, the lack of a controlled design in this study precludes the possibility of determining superiority between general psychodynamic group psychotherapy or an integrated therapy for agoraphobia; however, the integrated treatment specific to agoraphobia demonstrated promise.

Specific Phobia

To our knowledge no studies examining the efficacy of psychodynamic psychotherapy for specific phobia are available. Treatment of CCRTs may lead to the resolution of the phobic symptom, although this has not yet been empirically established.

Generally, although there is value in treating and understanding specific phobias psychodynamically, exposure is a more economical model of treating the symptoms of the condition.

Summary

Extant RCTs suggest that psychodynamic psychotherapy is an efficacious treatment for SAD, defined as having at least two RCTs conducted in independent research settings in which the treatment of interest is superior to no treatment, placebo, or alternative therapies or equivalent to a treatment already deemed efficacious [48]. With regard to GAD and PD, there have not been enough studies to form concrete conclusions regarding direct comparisons of psychodynamic psychotherapy and CBT [49]; however, the research we reviewed provides support for the possible efficacy of psychodynamic psychotherapy for GAD and PD with and without agoraphobia when compared to CBT.

In a systematic review, Leichsenring and colleagues [50] concluded that psychodynamic psychotherapy can be considered efficacious for SAD and possibly efficacious for GAD and PD. Our review corroborates this conclusion. Research employing rigorous study designs, examining treatments adapted for specific disorders, suggests that psychodynamic psychotherapy is as efficacious for anxiety disorders as other empirically supported treatments and generally continues to exert its effects from posttreatment to follow-up.

Future Directions

Research on psychodynamic psychotherapy for anxiety disorders is still scant compared to other psychotherapies, such as CBT. More RCTs are necessary to clarify the relative efficacy of psychodynamic psychotherapy compared to other active treatments. Furthermore, the continued use of meta-analytic methods is necessary to compare psychodynamic psychotherapy to other empirically supported psychotherapies [49]. Additionally, controlled studies that examine psychodynamic psychotherapy for specific phobias should be conducted.

Attention needs to be directed not just toward the quantity but also toward the quality of RCTs examining psychodynamic psychotherapy. In a quality-based review of RCTs of psychodynamic psychotherapy, Gerber and colleagues [51] concluded that many promising trials of psychodynamic psychotherapy compared the treatment to an inactive comparator rather than an empirically supported psychotherapy. Thus, more trials are needed that compare psychodynamic psychotherapy to an active treatment and that utilize quality designs and adequate sample sizes. In addition, researchers need to continue examining site-by-treatment interactions [33]. Such interactions are rarely examined but do occur, and exporting therapy

protocols to new sites, as well as differences between sites in supervision, can influence outcomes [33, 52]. It is unclear whether existing single-site trials that compared psychodynamic psychotherapy to another active treatment were negatively impacted by site-specific variables.

Additionally, given the centrality of the unconscious in psychodynamic models, future research should seek to utilize methods capable of observing change on this level. Implicit associations and functional neurological correlates of unconscious conflict might offer promise. For instance, one study found differences between self-reported self-esteem and implicit self-esteem in a socially anxious sample [53]. Furthermore, another study showed quantitative differences in the neural substrates of conscious versus unconscious control [54]. These studies illustrate the potential of applying contemporary research methodology to constructs relevant to psychodynamic theory.

There is also a glaring and problematic discrepancy between what psychodynamic psychotherapy aims to achieve and the variables that outcome studies typically assess [27]. The goal of psychodynamic psychotherapy extends beyond the reduction of acute symptoms, to the development of inner capacities that enable people to live life more flexibly and with a greater sense of possibility [27]. The outcome variables in the reviewed trials are generally constrained to the symptom level rather than tapping other constructs such as resilience, emotion regulation, fantasy life, increased self-reflectiveness, or increased self-understanding.

The restriction of outcome measures in RCTs to conscious, symptom-level variables is largely a result of the DSM, which defines psychiatric disorders based on symptoms. Because CBT aims to alleviate symptoms, CBT researchers initiated their outcome research using symptom reduction as a measure of treatment efficacy. Psychodynamic psychotherapy researchers, in an effort to model their studies after CBT RCTs and compare dynamic therapy to therapies already established as empirically supported, utilized the same outcome measures as their CBT research predecessors. However, whereas CBT aims to alleviate symptoms within a DSM framework, psychodynamic psychotherapy targets unconscious conflicts in addition to other outcomes (such as those detailed above). Such outcomes are not captured (or even addressed) by DSM diagnoses and may be more complicated to assess. It would be fruitful to learn whether psychodynamic psychotherapy indeed produces this kind of inner growth.

Recently, however, there has been movement away from outcomes based on symptoms alone. For example, new emphases on the network analysis and neurobiological underpinnings of psychological disorders (e.g., the National Institute of Health Research Domain Criteria (RDoC), [55]) seek to conceptualize outcomes beyond symptoms and DSM diagnoses. Recent interest in outcomes that are not constrained to the symptom level are more closely aligned with the changes sought in psychodynamic psychotherapy. In addition, the Patient-Centered Outcomes Research Institute funds studies in which outcomes are centered around what patients believe is important to them and not just symptoms. For instance, patients with panic disorder may want to understand the meaning and origins of their panic

attacks in addition to feeling less anxious. Psychodynamic psychotherapy may be at least as efficacious compared to CBT on these outcomes and potentially more efficacious when compared to pharmacotherapy.

Future research focused on creating a unified psychodynamic treatment for anxiety disorders, comparing it to transdiagnostic CBTs, and assessing transdiagnostic psychic processes such as those outlined in RDoC or by Shedler [27] would be informative. Leichsenring and Salzer [26, 56] proposed a *transdiagnostic protocol* that consists of seven modules addressing topics such as socialization of the patient to therapy, establishing treatment goals and a secure helping alliance, identifying the core conflict, modifying underlying defenses and the underlying response of the self, and processing termination. This treatment, which integrates the most efficacious methods of psychodynamic psychotherapy into a broadly applicable protocol, parallels Barlow and colleague's unified protocol for emotional disorders [57]. Leichsenring and colleagues plan to test this protocol using a controlled multisite design.

Future theory development and research might also consider integrating psychodynamic and cognitive-behavioral conceptualizations and treatments. Although psychodynamic and cognitive-behavioral conceptualizations and interventions are different, they are far from incompatible. For instance, avoidance of feared situations can be viewed as a safety behavior (CBT) or a defense mechanism (psychodynamic). Furthermore, embedded in cognitive-behavioral models is the theory akin to unconscious psychic conflict [58]. For example, in their gold standard treatment for SAD, Hope et al. [59] describe core beliefs as something often outside the patient's awareness: "Even though the layers underneath have always been there, you may not be able to see them until you remove the outer layers" (p. 207). In CBT, as in psychodynamic theory, patients are believed to be largely unaware of central parts of their psyche. Although CBT does not give as much emphasis to changing these deeper psychic structures (compared to conscious automatic thoughts, for instance), there are conceptual parallels between this component of the therapy and psychodynamic psychotherapy.

Empirical results suggest that integrative treatments may have promise [46]. Psychodynamic clinicians may consider using cognitive-behavioral techniques (rather than pharmacotherapy) to reduce acute anxiety symptoms before delving into conflict-related work aimed at reducing patients' vulnerability to symptoms. Psychodynamic conceptualizations may also help guide exposures in CBT. For example, the understanding that attachment fears underpin panic symptoms may enhance CBT for PD with agoraphobia. When guiding an interoceptive exposure for panic, for instance, the therapist could temporarily leave the patient alone so as to potentiate habituation to the feared separation in addition to the physiological arousal. Though a full integrative model is out of the scope of this chapter, future theories conceptualizing anxiety disorders could expand upon these ideas, and proposed integrative approaches should ultimately be subjected to scientific inquiry.

Conclusions

Over the last three decades, academic psychologists have largely contended that psychodynamic psychotherapy is unscientific. However, the literature reviewed in this paper suggests that this narrative is misguided, at least as it pertains to anxiety disorders. In addition, as the field moves away from using symptom-driven criteria to define treatment outcomes, psychodynamic therapy may demonstrate even greater efficacy.

The increasing balkanization of psychology limits the advancement of psychotherapy. Though empirically supported treatments for anxiety disorders help people, a large proportion of patients do not remit. Thus, there is much work to be done, and dogmatic allegiance to particular theoretical approaches stifles conversation that could advance the common project of helping those who suffer. There is a need to shift the field of psychology away from its current state of divisiveness, toward productive collaboration and a new commitment to pragmatism.

References

1. Freud S. On the grounds for detaching a particular syndrome from neurasthenia under the description 'anxiety neurosis'. In: Strachey J, et al., editors. The standard edition of the complete psychological works of Sigmund Freud, vol. 3. London: Hogarth Press; 1894. p. 85–115.
2. Freud S. Interpretation of dreams. In: Strachey J, et al., editors. The standard edition of the complete psychological works of Sigmund Freud, vol. 4. London: Hogarth Press; 1900. p. ix–627.
3. Freud S. The unconscious. In: Strachey J, et al., editors. The standard edition of the complete psychological works of Sigmund Freud, vol. 8. London: Hogarth Press; 1915. p. 159–215.
4. Freud S. The Ego and the Id. In: Strachey J, et al., editors. The standard edition of the complete psychological works of Sigmund Freud, vol. 19. London: Hogarth Press; 1923. p. 1–66.
5. Freud S. Inhibitions, symptoms and anxiety. In: Strachey J, et al., editors. The standard edition of the complete psychological works of Sigmund Freud, vol. 20. London: Hogarth Press; 1926. p. 75–176.
6. Klein M. Notes on some schizoid mechanisms. Int J Psychoanal. 1946;27:99.
7. Klein M. A contribution to the theory of anxiety and guilt. Int J Psychoanal. 1948;29:114–23.
8. Klein M. Some theoretical conclusions regarding the emotional life of the infant. In: The writings of Melanie Klein volume 8: envy and gratitude and other works. London: Hogarth Press; 1952. p. 61–94.
9. Winnicott DW. The maturational processes and the facilitating environment: studies in the theory of emotional development. New York: International Universities Press; 1965.
10. Kohut H. The analysis of the self. Chicago: The University of Chicago Press; 1971.
11. Kohut H. The restoration of the self. New York: International University Press; 1977.
12. Greenberg JR, Mitchell SA. Object relations in psychoanalytic theory. Cambridge, MA: Harvard University Press; 1983.

13. Leichsenring F, Klein S, Salzer S. Psychodynamic therapy of anxiety disorders. The Wiley handbook of anxiety disorders: Wiley; 2014. p. 852–64. https://doi.org/10.1002/9781118775349.ch42.

14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.

15. Shear MK, Cooper AM, Klerman GL, Busch FN, Shapiro T. A psychodynamic model of panic disorder. Am J Psychiatry. 1993;150:859–86.

16. Busch FN, Milrod BL, Singer MB. Theory and technique in psychodynamic treatment of panic disorder. Am J Psychother. 1999;8:234–42.

17. Leichsenring F, Beutel M, Leibing E. Psychodynamic psychotherapy for social phobia: a treatment manual based on supportive–expressive therapy. Bull Menninger Clin. Guilford Publications. 2007;71(1):56–84. https://doi.org/10.1521/bumc.2007.71.1.56.

18. Luborsky L. Principles of psychoanalytic psychotherapy: manual for supportive-expressive treatment. New York: Basic Books; 1984.

19. Crits-Christoph P, Crits-Christoph K, Wolf-Palacio D, Fichter M, Rudick D. Brief supportive-expressive psychodynamic therapy for generalized anxiety disorder. In: Barber JP, Crits-Christoph P, editors. Dynamic therapies for psychiatric disorders (Axis I). New York: Basic Books; 1995. p. 43–83.

20. Cassidy J, Lichtenstein-Phelps J, Sibrava NJ, Thomas CL, Borkovec TD. Generalized anxiety disorder: connections with self-reported attachment. Behav Ther. Elsevier BV. 2009;40(1):23–38. https://doi.org/10.1016/j.beth.2007.12.004.

21. Busch FN, Milrod BL. Generalized anxiety disorder and other anxiety disorders. In: Luyten P, Mayes LC, Fonagy P, Target M, Blatt SJ, editors. Handbook of psychodynamic approaches to psychopathology. New York: Guilford Press; 2015. p. 152–64.

22. Crits-Christoph P. Psychodynamic-interpersonal treatment of generalized anxiety disorder. Clinical psychology. Sci Pract [Internet]. Wiley. 2002;9(1):81–4. https://doi.org/10.1093/clipsy/9.1.81.

23. Busch FN, Milrod BL, Singer MB, Aronson AC. Psychoanalytic inquiry book series. Manual of panic focused psychodynamic psychotherapy—eXtended range. New York: Routledge/Taylor & Francis Group; 2012.

24. Milrod B. Emptiness in agoraphobia patients. J Am Psychoanal Assoc. 2007;55:1007–26.

25. Barber JP, Luborsky L. A psychodynamic view of simple phobias and prescriptive matching: a commentary. Psychotherapy (Chic). 1991;28:469–72.

26. Leichsenring F, Steinert C. Towards an evidence-based unified psychodynamic protocol for emotional disorders. J Affect Disord. 2018;232:400–16.

27. Shedler J. The efficacy of psychodynamic psychotherapy. Am Psychol. 2010;65(2):98–109.

28. Bandelow B, Reitt M, Röver C, Michaelis S, Görlich Y, Wedekind D. Efficacy of treatments for anxiety disorders. Int Clin Psychopharmacol. Ovid Technologies (Wolters Kluwer Health). 2015;30(4):183–92. https://doi.org/10.1097/yic.0000000000000078.

29. Keefe JR, McCarthy KS, Dinger U, Zilcha-Mano S, Barber JP. A meta-analytic review of psychodynamic therapies for anxiety disorders. Clin Psychol Rev. Elsevier BV. 2014;34(4):309–23. https://doi.org/10.1016/j.cpr.2014.03.004.

30. Milrod B, Busch F, Leon AC, Aronson A, Roiphe J, Rudden M, et al. A pilot open trial of brief psychodynamic psychotherapy for panic disorder. J Psychother Pract Res. 2001;10:239–45.

31. Milrod B, Busch F, Cooper A, Shapiro T. Manual of panic-focused psychodynamic psychotherapy. Washington, DC: American Psychiatric Press; 1997.

32. Milrod B, Leon AC, Busch F, Rudden M, Schwalberg M, Clarkin J, Aronson A, Singer M, Turchin W, Klass ET, Graf E. A randomized controlled clinical trial of psychoanalytic psychotherapy for panic disorder. Am J Psychiatry. American Psychiatric Association Publishing. 2007;164(2):265. https://doi.org/10.1176/appi.ajp.164.2.265.

33. Milrod B, Chambless DL, Gallop R, Busch FN, Schwalberg M, McCarthy KS, et al. Psychotherapies for panic disorder: a tale of two sites. J Clin Psychiatry. 2016;77:927–35. https://doi.org/10.4088/JCP.14m09507.

34. Leichsenring F, Salzer S, Beutel ME, Herpertz S, Hiller W, Hoyer J, Huesing J, Joraschky P, Nolting B, Poehlmann K, Ritter V, Stangier U, Strauss B, Stuhldreher N, Tefikow S, Teismann T, Willutzki U, Wiltink J, Leibing E. Psychodynamic therapy and cognitive behavioral therapy in social anxiety disorder: a multicenter randomized controlled trial. Am J Psychiatry. 2013;170:759–67.

35. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.

36. Clark DM, Wells A. A cognitive model of social phobia. In: Heimberg RG, Liebowitz MR, Hope DA, Schneier FR, editors. Social phobia: diagnosis, assessment, and treatment. New York: Guilford Press; 1995. p. 69–93.

37. Leichsenring F, Salzer S, Beutel ME, Herpertz S, Hiller W, Hoyer J, et al. Long-term outcome of psychodynamic therapy and cognitive-behavioral therapy in social anxiety disorder. Am J Psychiatry. American Psychiatric Publishing. 2014;171(10):1074–82. https://doi.org/10.1176/appi.ajp.2014.13111514.

38. Bögels SM, Wijts P, Oort FJ, Sallaerts SJM. Psychodynamic psychotherapy versus cognitive behavior therapy for social anxiety disorder: An efficacy and partial effectiveness trial. Depress Anxiety. [Internet]. Wiley. 2014;31(5):363–73. https://doi.org/10.1002/da.22246.

39. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. American Psychological Association (APA). 1991;59(1):12–9. https://doi.org/10.1037/0022-006x.59.1.12.

40. Johansson R, Hesslow T, Ljótsson B, Jansson A, Jonsson L, Färdig S, et al. Internet-based affect-focused psychodynamic therapy for social anxiety disorder: a randomized controlled trial with 2-year follow-up. Psychotherapy. American Psychological Association (APA). 2017;54(4):351–60. https://doi.org/10.1037/pst0000147.

41. Crits-Christoph P, Connolly MB, Azarian K, Crits-Christoph K, Shappell S. An open trial of brief supportive-expressive psychotherapy in the treatment of generalized anxiety disorder. Psychotherapy (Chic). American Psychological Association (APA). 1996;33(3):418–30. https://doi.org/10.1037/0033-3204.33.3.418.

42. Crits-Christoph P, Gibbons MBC, Narducci J, Schamberger M, Gallop R. Interpersonal problems and the outcome of interpersonally oriented psychodynamic treatment of GAD. Psychotherapy (Chic) American Psychological Association (APA). 2005;42(2):211–24. https://doi.org/10.1037/0033-3204.42.2.211.

43. Leichsenring F, Salzer S, Jaeger U, Kachele H, Kreische R, Leweke F, et al. Short-term psychodynamic psychotherapy and cognitive-behavioral therapy in generalized anxiety disorder: a randomized, controlled trial. Am J Psychiatry. American Psychiatric Publishing. 2009;166(8):875–81. https://doi.org/10.1176/appi.ajp.2009.09030441.

44. Salzer S, Winkelbach C, Leweke F, Leibing E, Leichsenring F. Long-term effects of short-term psychodynamic psychotherapy and cognitive-behavioural therapy in generalized anxiety disorder: 12-month follow-up. Can J Psychiatry. SAGE Publications. 2011;56(8):503–8. https://doi.org/10.1177/070674371105600809.

45. Andersson G, Paxling B, Roch-Norlund P, Östman G, Norgren A, Almlöv J, et al. Internet-based psychodynamic versus cognitive behavioral guided self-help for generalized anxiety disorder: a randomized controlled trial. Psychother Psychosom. S. Karger AG. 2012;81(6):344–55. https://doi.org/10.1159/000339371.

46. Hoffart A, Matinsen EW. Exposure-based integrated vs. pure psychodynamic treatment of agoraphobic inpatients. Psychotherapy (Chic). American Psychological Association (APA). 1990;27(2):210–8. https://doi.org/10.1037/0033-3204.27.2.210.

47. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Rev 3rd ed. Washington, DC: American Psychiatric Association; 1987.

48. Chambless DL, Hollon SD. Defining empirically supported therapies. J Consult Clin Psychol. American Psychological Association (APA). 1998;66(1):7–18. https://doi.org/10.1037/0022-006x.66.1.7.

49. Cuijpers P, Sijbrandij M, Koole S, Huibers M, Berking M, Andersson G. Psychological treatment of generalized anxiety disorder: a meta-analysis. Clin Psychol Rev. Elsevier BV. 2014;34(2):130–40. https://doi.org/10.1016/j.cpr.2014.01.002.
50. Leichsenring F, Leweke F, Kleine S, Steinert C. The empirical status of psychodynamic psychotherapy–an update: Bambi's alive and kicking. Psychother Psychosom. 2015;84(3):129–48.
51. Gerber AJ, Kocsis JH, Milrod BL, Roose SP, Barber JP, Thase ME, et al. A quality-based review of randomized controlled trials of psychodynamic psychotherapy. Am J Psychiatry. American Psychiatric Publishing. 2011;168(1):19–28. https://doi.org/10.1176/appi.ajp.2010.08060843.
52. Luborsky L, Diguer L, Seligman DA, Rosenthal R, Krause ED, Johnson S, et al. The researcher's own therapy allegiances: a "wild card" in comparisons of treatment efficacy. Clin Psychol (New York). 1999;6:95–106. https://doi.org/10.1093/clipsy.6.1.95.
53. de Jong PJ. Implicit self-esteem and social anxiety: differential self-favouring effects in high and low anxious individuals. Behav Res Ther. 2002;40:501–8. https://doi.org/10.1016/S0005-7967(01)00022-5.
54. Jiang J, Bailey K, Xiang L, Zhang L, Zhang Q. Comparing the neural correlates of conscious and unconscious conflict control in a masked Stroop priming task. Front Hum Neurosci. 2016;10:297. https://doi.org/10.3389/fnhum.2016.00297.
55. Clark LA, Cuthbert B, Lewis-Fernández R, Narrow WE, Reed GM. Three approaches to understanding and classifying mental disorder: ICD-11, DSM-5, and the National Institute of Mental Health's research domain criteria (RDoC). Psychol Sci Public Interest. 2017;18:72–145.
56. Leichsenring F, Salzer S. A unified protocol for the transdiagnostic psychodynamic treatment of anxiety disorders: an evidence-based approach. Psychotherapy. American Psychological Association (APA). 2014;51(2):224–45. https://doi.org/10.1037/a0033815.
57. Barlow DH, Farchione TJ, Fairholme CP, Ellard KK, Boisseau CL, Allen LB, et al. Unified protocol for transdiagnostic treatment of emotional disorders: Oxford University Press; 2010. https://doi.org/10.1093/med:psych/9780199772667.001.0001.
58. Cohen JN, McElhaney R, Jensen D. The empirical examinability of psychodynamic psychotherapy: a reply to Hoffart and Johnson. Clin Psychol Sci. 2018;6:458–63. https://doi.org/10.1177/2167702617751887.
59. Hope DA, Heimberg RG, Turk CL. Managing social anxiety: a cognitive-behavioral therapy approach. New York: Oxford University Press; 2010.

Chapter 18
Barriers to Implementing Evidence-Based Treatments for Anxiety Disorders in Community Settings

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Anxiety disorders are one of the most prevalent mental disorders in the United States, with one in every three people having been diagnosed with an anxiety disorder at some point during their lifetime [1]. Evidence-based treatments (EBTs), such as cognitive behavioral therapy (CBT), have been developed and proven to effectively treat a variety of anxiety disorders [2, 3]. However, less than half of individuals with an anxiety disorder receive any care for their anxiety, and fewer than 10% receive evidence-based treatments [4]. This disparity reflects the science-practice gap: a 17-year lag time between the time EBTs are developed and when they are employed in routine practice, such as in community mental health settings [5–7].

In the last few decades, implementation science (IS) has emerged as an innovative and effective method of addressing the science-practice gap in mental health treatment [8]. IS systematically assesses the integration and uptake of EBTs into routine clinical care with the goal of improving the quality and effectiveness of health care provided in community settings [9]. IS explores the factors that challenge and facilitate the integration of EBTs in community settings, emphasizing the examination of these barriers and facilitators at multiple levels, such as at the organization, provider, treatment, and patient levels [10, 11]. Understanding the multilevel barriers and challenges that impact the integration of EBTs into routine clinical settings can help facilitate long-term sustainability of EBTs in community settings.

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In this chapter, we will review the most common factors, including barriers (Table 18.1) and facilitators (Table 18.2), that have been shown to impact the integration, use, and long-term sustainability of EBTs in community settings. This information can be used to help community providers be aware of frequently emerging difficulties when implementing EBTs in their routine practice, as well as provide some guidelines on how to address these challenges.

Barriers to Implementing EBTs in Community Settings

Organization-Level Barriers

Organization-level barriers refer to the challenges related to the structural, political, and cultural context through which an intervention proceeds [10]. In other words, these challenges are related to the implementation setting itself, such as the organization's climate and culture, available resources, and existing structures. These types of barriers represent some of the first major challenges faced when implementing EBTs in community settings [12], as the decision to adopt EBTs into clinical practice is typically determined at the organizational level.

Organization Climate and Culture

Some of the most frequently cited organization-level barriers are climate and culture, which refer to the interactions between employees and the overall environment of the workplace [13]. Specifically, an organization's climate refers to the day-to-day, practices, procedures, and routines that employees experience, while culture refers to the organizations' beliefs and values [13]. Together, organization climate and culture can pose a significant challenge to the implementation of EBTs for anxiety disorders by impacting an organization's decision to adopt or implement new treatment interventions [14]. Research shows that poor organization climate and culture, such as having colleagues or leadership teams that are skeptical of new treatments, can impact other team members' views toward EBTs. For example, even if individual providers are interested in learning more about and possibly adopting EBTs to help their patients, or they may approach EBTs with skepticism when working in organizations that have poor climate and culture [14].

Another significant organization-level barrier is misalignment, or the mismatch between the meaning and values attached to a given intervention, and the norms, values, and priorities of the organization [10, 15]. For example, misalignment might occur when an intervention requires extended session lengths to accommodate the mechanisms of change (e.g., exposure sessions for the treatment of panic disorder), but the organization's structure and scheduling do not allow for such extension due to resource, space, or scheduling constraints. Misalignment can result in organiza-

Table 18.1 Barriers to implementing evidence-based treatments (EBTs) in community settings by implementation level

Barrier type	Examples
Organizational-level barriers: Challenges related to the structural, political, and cultural context through which an intervention proceeds	
Organization climate and culture	Colleagues' skepticism about EBT interventions
	Organizational misalignment about the EBT intervention
	Designating EBTs as a lower priority than other services
	Providing little support for EBT use
Resource availability	Lack of time
	Lack of space
	Lack of human capital
Existing structures	Mandate to use EBT originates at the administrator level
	Limited discussion with frontline service providers about changes in policies
	Providers have difficulty adopting top-down EBT mandates
Provider-level barriers: Characteristics of the individuals who are responsible for providing the intervention	
Perceptions	Narrow definitions of EBTs
	Negative attitudes toward EBTs
	Belief that EBTs cannot address the complex needs of patients
Skills and abilities	Difficulties implementing EBTs with skill and competence
Burnout	Providers' heavy workload
	Providers' complex caseload
Treatment-level barriers: Challenges that emerge due to the intervention's characteristics	
Structure	Rigid time allocation within treatment sessions
	Expectation and necessity of completing homework assignments
Delivery	Required regular patient attendance
	Technology-based EBTs challenge the therapeutic relationship
Content	Single-diagnosis focus of EBTs
	Clinical jargon or stiff language
	Culturally insensitive materials
Patient-level barriers: Challenges specific to the patient that impact treatment implementation	
Knowledge and beliefs	Belief that mental health is not a real medical concern
	Misinterpretation or suspicion of treatment
Attendance	Missing treatment appointments
	Difficulties remembering the content of the previous session
Background	Patient's background, including culture and preferences, misaligned with treatment materials

Table 18.2 Strategies to address barriers to implementation of evidence-based treatments (EBTs) in community settings

Strategy	Definition	Strategic Steps
Community-based participatory research	Innovative framework in implementation science Cultivates equitable partnerships between community members, organizational representatives, and researchers in all aspects of the research process	Highlight the strengths among partners
		Ensure shared responsibilities during implementation
		Recognize the community as its own entity
		Harness community wisdom
		Build upon existing strengths and resources
		Promote co-learning
		Increase sustainability of EBTs
		Cultivate participant engagement
		Utilize an interactive process
		Leverage relationship to overcome barriers
Organizational buy-in	Engendered support (e.g., space, time, capital, and other resources available) of organizations Stakeholders' belief that EBTs offer more advantages than disadvantages	Assess alignment between EBT and organization's priorities
		Assess that EBT is aligned with patients' needs
		Frame EBT as an added value
		Present EBT's cost-effectiveness
		Show EBT's ability to ease duties
		Foster explicit communication
		State clear expectations
Resource support	Resource facilitation (e.g., interactive and noninteractive resources)	Identify resources needed prior and during EBT implementation
		Provide interactive resources (e.g., workshops, workgroups, and consultation)
		Provide non-integrative resources (e.g., access to libraries, news and updates from the field, and archived talks/slides)
Champions	Members of the organization who: Are respected sources of information Are integrated with their peers in the organization Possess high enthusiasm for the intervention	Establish the role of the champion
		Ensure agreement about who the champion should be
		Have champions at multiple levels within the organization
		Provide incentives for champions

tions designating EBTs as a lower priority than other services [16], providing little support for the use of EBT interventions in routine practice [15], and difficulties changing existing practices [17]. Thus, misalignment across levels in the organization may inhibit the successful integration and long-term use of EBTs in organizations [18].

Resource Availability

Lack of resources (e.g., time, space, finances, and staff) is another organization-level barrier that can hinder implementation [19] and an organization's readiness for change [16]. The allocation of time for new initiatives, such as EBTs, is particularly challenging in community settings, where providers frequently find themselves overbooked, having limited session time (e.g., 35–40 minutes) to review all necessary clinical information as well as deliver EBT content that is usually intended to be delivered in longer amounts of time (e.g., 45–60 minutes) [20] and unable to allocate time to attend recommended supervision and consultation hours to support the EBT delivery [21]. Thus, organizations wanting to integrate EBTs into their care have had to make adjustments to accommodate these time-related constraints, such as providers scheduling EBT-related training sessions during time slots generally held for other activities [16], walk-ins, or ground rounds [20].

In addition to time, many community organizations also lack the physical space necessary to deliver EBTs, such as availability of a room to deliver a 50-minute individual session. These types of space constraints have led providers to deliver EBT interventions in spaces usually designated for other uses, such as nurses' rooms, lunchrooms or kitchens, and consultation rooms in neighboring clinics outside of the main site [15].

The lack of human capital, or individuals within the organization with skills, knowledge, and experience to deliver an intervention, is another resource-related organizational barrier in community settings [19, 22]. Community organizations face shortages of staff who have the experience to train, supervise, and deliver EBTs, typically due to the prevalence of part-time providers delivering mental health care and high rates of staff turnover in community settings [8]. As a result, community organizations find it challenging to appropriately train and engage new providers in EBTs [15], which, in turn, limits their long-term sustainability [8].

Existing Structures

The last common organization-level barrier to implementing EBTs relates to the existing structures within an organization, such as the systems, mandates, policies, and regulations within an organization [23–25]. Research has shown that generally, the decision to implement an EBT within an organization occurs at the administrator level, with limited previous discussion with frontline service providers or consideration of existing providers' needs or knowledge of EBTs [17]. This type of top-down mandate to adopt an EBT often hinders successful implementation by leading to providers' challenges in adopting the EBT which results in providers using the interventions with fewer than 75% of their caseloads [26]. Specific emergent challenges faced by providers when a top-down mandate occurs include unmanageable workloads, increased frustration, and feeling pressured to work extra

hours during their lunch hours or after work to cover all their assigned cases [16, 27]. Thus, top-down mandates can reflect weak organizational climate and culture, increase the likelihood of misalignment, and reduce the long-term sustainability and usage of EBTs.

Provider-Level Barriers

Provider-level barriers refer to the characteristics of the individuals who are responsible for providing the intervention that impacts the effective implementation of EBTs in community settings [10, 12, 28] and include providers' negative perceptions toward EBTs, training-related difficulties, and burnout.

Perceptions

Providers' perceptions, or their beliefs, demeanor, and actions, can be a major barrier in implementing EBTs in community settings [11, 29–31]. Studies show that both positive and negative attitudes effect provider's willingness to learn and adopt an EBT, even prior to EBT training [18]. Particularly in community settings, data suggest that many providers hold narrow definitions and negative attitudes toward EBT use [31, 32], including skepticism over the generalizability of efficacy results [31, 32], perceived rigidness of EBT protocols [29], uncertainty regarding the cost-benefit of using EBTs, and doubt regarding the ability of EBTs to be effective in diverse complex settings [16]. These negative attitudes can also indirectly decrease the likelihood of EBT use in the community, because providers' negative attitudes may inadvertently get transferred to their patients, resulting in increased uncertainty about EBTs even among patients [16].

Reports show that even when providers are knowledgeable about the evidence supporting EBTs and believe that EBTs could be helpful for some of their patients, they are still unlikely to adopt EBTs if they believe the invention is ill-suited for their patients [25]. For example, many providers in community settings believe that EBTs are unable to fit specific cultural needs [33], cannot address comorbidity or complex cases [34, 35], and will actually worsen their patients' symptoms during treatment [36–39]. As a result of these beliefs, there is reduced motivation among providers to use EBTs because of the perception that EBTs are not helpful for their particular patients [40].

Skills and Ability

Given that there is often a lack of "expert" mental health specialists in community settings, provider skills and ability can pose a significant challenge to implementation efforts [41, 42]. Initial training and booster sessions are typically conducted

during EBT implementation to help equip staff [21, 42], but providers have reported difficulties implementing EBTs with skill and competence [21]. For instance, providers described feeling unsure when it is acceptable to make adaptations to the EBT protocols, such as simplifying language and reordering content [20], and feeling as though they lack the fundamental skills needed to address complex patient needs [40]. This leads to providers adapting treatments using a trial-and-error method that often results in the exclusion of core elements that are paramount to treatment efficacy [43]. This exclusion of elements can hinder EBT fidelity, worsen negative attitudes about EBT flexibility, and decrease motivation to continue using EBTs [18, 44].

Burnout

Provider burnout is another major problem affecting the implementation of EBTs in community settings [45, 46]. Burnout refers to the emotional exhaustion, depersonalization, and deflated sense of self-efficacy caused by job-related stressors [47]. Studies show that between 21% and 67% of mental health providers experience burnout [48], with community-based providers being at an increased risk [12, 49, 50]. Data suggest that the already high levels of burnout present in community settings may affect a provider's enthusiasm about a new intervention, limiting their willingness to expend their efforts to learn how to deliver a new EBT [48]. When an EBT is introduced into the organization, many providers have stated that the implementation of EBTs at times may lead to an immediate increase in burden, due to lack of training and support and demanding logistics required to implement EBTs [12]. As a result, providers have reported feeling incapable, exhausted, and cynical about EBTs [51].

One of the main contributing factors to burnout among providers is workload [12], frequently conceptualized as a provider's total work including caseload, number of EBTs delivered, and weekly hours of EBT-related activities including outcome monitoring, travel time for client contact, and receiving supervision/consultation [52]. Research shows that higher caseloads, more EBTs delivered, and total hours worked predict provider burnout [52]. This is a major challenge in community settings as providers have larger caseloads compared to providers who are part of treatment efficacy trials, which frequently include doctoral students working with small focused caseloads with no expected productivity quota. In addition to carrying exceptionally large caseloads [11], providers in community settings typically see very complex cases that can create an additional burden (e.g., comorbidity, complex life circumstances, racially and ethnically diverse; [53]). Provider burnout is a major barrier to the implementation of EBTs in community settings because high provider burnout decreases motivation to learn and willingness to engage in EBTs [54], leads to more negative attitudes toward EBTs [55], and it is a major contributing factor to high (more than 25%) staff turnover per year [56].

Treatment-Level Barriers

When implementing EBTs in real-world settings, considerable barriers also exist at the treatment level. Treatment-level barriers refer to challenges that emerge as a result of the intervention's characteristics, such as treatment structure, delivery method, and content [10, 20, 57]. Treatment-level barriers can be problematic when organizations or individuals attempt to integrate EBTs that are rigid into routine practice.

Structure

Interventions typically considered rigid include structured or manualized EBTs. Manualized EBTs are commonly characterized as having a specific in-session structures that include setting session-specific goals, teaching prescribed sets of strategies, and discussing content material. For example, during a 45-minute session, clinicians may be tasked with reviewing work completed by a patient between sessions, introducing a new concept, completing a worksheet with the patient, and assigning homework for the patient to complete before the next session. Meeting the requirements of these structured protocols can be particularly difficult when treating patients seen in community settings, who frequently present with pressing external circumstances, such as financial, relational, or medical crises [16, 20]. Manualized treatments rarely include allocated time for these emerging topic conversations, leaving providers with the challenge of trying to cover the session content and balance the needs of patients facing difficult life circumstances, such as loss of a loved one [20]. Following these sessions, providers note that even an extra 5 minutes within the treatment structure would have allowed them to better address some of the patient's external needs [20].

Another common challenge of manualized treatments is related to out-of-session structure, such as homework assignments that patients are expected to regularly complete between sessions. Despite homework assignments being frequently regarded as a core component of treatment, homework adherence can be especially difficult when treating patients in community settings who live in unstable or chaotic conditions. Research suggests that allocating space and time to complete between session activities and practice material covered during session becomes arduous for patients that experience turbulent living situations [57]. Thus, the expectation and necessity of completing homework assignments can be impractical or burdensome for many individuals with anxiety in community settings.

Delivery

Another core component of many structured EBTs that can pose a significant challenge to community implementation efforts is regular delivery of the EBT. Typically, EBTs require that providers deliver 12–16 weekly sessions over the course of treat-

ment, but patients in community settings frequently have difficulties attending the required number of sessions at the recommended frequency (i.e. once a week) (e.g., [58, 59]). For this population, attending weekly treatment sessions may be a difficult treatment expectation as high levels of anxiety are associated with the desire to avoid situations that bring them discomfort. Thus, patients may avoid sessions knowing that they will be asked to discuss their feelings or even experience some minimal discomfort during exposure exercises. Since many EBTs are required to be delivered weekly, patients who do not regularly attend may not complete the full dose of sessions and therefore risk not receiving the full benefit of treatment [60]. This delivery format can be more challenging when treating patients in low-resource community settings who frequently miss appointments due to external barriers such as transportation costs [23]. Despite the fact that some EBTs have used technology and mobile devices as a possible way to address this delivery-related difficulty, providers have highlighted added difficulties that emerge related to this solution, such as challenges building the therapeutic relationship through technology-assisted interfaces without having the ability to work with patients face-to-face [20]. The need for EBTs to be delivered in a traditional, highly structured format to be potent can be daunting or even impractical for organizations, providers, and patients, thus threatening the use of these treatments in community settings.

Content

Manualized EBTs have also been perceived as having a narrow focus of content material. Most EBTs are designed to address a single diagnosis (e.g., generalized anxiety disorder, panic disorder) and do not provide enough guidance for how to handle co-occurring mental or health conditions [61]. For example, many manualized treatments for anxiety do not provide guidance on how to choose which problematic symptoms to address first when treating a patient has both anxiety and depression (e.g., [62]), which is commonly the case in patients presenting in community settings [63]. In these circumstances, providers must frequently rely on their own clinical judgment to determine how to best treat the patient, which can beget additional challenges (see prior section on provider skills and abilities). Due to these difficulties, new transdiagnostic approaches intended to treat complex patients presenting with diverse symptomology have recently become more popular [64], but even these treatments fail to address comorbid physical health conditions regularly experienced by patients seen in community settings. Individuals who struggle with comorbid physical health problems may require extra support or a different method to complete some treatment exercises. Rigid treatment content commonly results in comorbidities left unaddressed in session which can affect the likelihood of patients regularly attending or benefiting from treatment [16, 20].

Additional treatment content-related barriers arise when treating patients of diverse backgrounds. Manuals or treatments often contain clinical jargon or stiff language that make it difficult for individuals with less education or limited literacy

to understand the material [20]. In these cases, therapists must simplify the language to ensure that patients comprehend the concepts being taught. In addition to diverse literacy levels, patients in community settings tend to have cultural backgrounds that differ from the majority of patients included in efficacy trials of EBTs. Therefore, EBTs have regularly been found to be culturally insensitive and providers have been known to advocate for needed modifications [33]. For example, one study treating veterans found that questions within manualized EBTs were ill-suited for patients and changes had to be made to increase relevance [57]. Due to a lack of guidance for how to handle both internal and external issues faced by patients of diverse backgrounds and needs [18, 20], manualized EBTs are frequently perceived as inflexible, rigid, and difficult to implement within community settings [18, 29].

Patient-Level Barriers

The final category of barriers is patient-level barriers, which refer to any challenges specific to the patient that impact treatment implementation [10]. Some of these barriers include patients' knowledge and beliefs, attendance, and background.

Knowledge and Beliefs

Beliefs refer to patients' perceptions about treatment and can hinder their seeking and engaging in treatment. Some individuals believe that mental health is a sign of moral weakness or not a "real" medical concern, which can impact their decision to initiate treatment. Additionally, treatment-related beliefs may impact the types of treatments that patients receive from their providers. For example, patients who are not aware of EBTs or may have misperceptions of what EBTs encompass may be less likely to request these types of treatments from their providers and organizations. Lack of information can also lead to misinterpretation and suspicion of the treatment and its outcomes; patients doubting whether homework is actually beneficial to them may have lower homework adherence and ultimately challenge the effectiveness of the treatment [20].

Attendance

Another frequently cited patient-level barrier is treatment attendance (i.e., attending the designated number of sessions required in an EBT) [15, 20, 58, 59]. Research shows that patients in community settings often have difficulty consistently attending weekly scheduled sessions and have inconsistent frequency and consistency in attendance (e.g., [58, 59]). This can be problematic as evidence shows that missing appointments can decrease patients' enthusiasm and engagement in the treatment [15]. Additionally, frequent "no-showing" makes it challenging for both the provider and the patient to recall what happened during the previous session and con-

tinue to build upon previously learned constructs [20]. Instead, session time may be spent "catching up" and re-reviewing materials covered in earlier sessions, which can delay treatment completion and patient's improvement.

Background

There are also patient-level barriers to treatment that arise due to patients' backgrounds including cultural factors and prior experiences. An individual's background can impact their ability to relate to the treatment material. For instance, one study showed that patients from working-class backgrounds were more likely to have difficulties applying mindfulness-based activities to their daily life, wondering how the skill would help them address emergent life stressors [65]. Disconnect between a patient's background and the treatment material may hinder treatment effectiveness as patients may be less willing to participate or complete required activities. Additional stylistic preferences toward certain aspects of treatment such as format may also affect treatment. Depending on individual dispositions, patients may have more difficulty attending group treatments and may perceive them as less helpful [65] compared to individual treatments. For example, some patients that have attended group treatment have reported wanting individual face-to-face time with the therapist, an aspect that typically occurs in individual treatment, while other patients preferred the "drop-in nature of the group" and not having mandatory check-ins or attendance restrictions [65].

Strategies to Address Barriers to Implementation

In recent years, there has been an increasing effort to develop research designs that address barriers and leverage facilitators to implementing EBTs, with the goal of accelerating the translation of research findings into routine practice [66]. As previously stated, implementation-related barriers occur at multilevels; thus, it is crucial to implement strategies and facilitators that address these challenges in a multilevel manner. Some of the strategies that can be implemented to effectively address many of the aforementioned barriers [12, 67, 68] include conducting community-based participatory research (CBPR), obtaining organizational buy-in, providing resource facilitation, and utilizing champions (Table 18.2).

Community-Based Participatory Research (CBPR)

Community-based participatory research (CBPR) is an innovative framework within implementation science that cultivates equitable partnerships between community members, organizational representatives, and researchers in all

aspects of the research process including knowledge development, dissemination, and integration of research results [69]. The goal of CBPR is to highlight the strengths among partners and ensure shared responsibilities during implementation [70]. Core principles of CBPR recognize the community as its own entity rather than a setting or location, harness community wisdom, and build upon existing strengths and resources within the community to promote co-learning and an iterative process that allows for a long-term committed partnership [71, 72]. One exemplar CBPR partnership, highlighted by Youn and colleagues, was established to disrupt the cycle of recidivism among high-risk young men by enhancing emotion regulation skills. Throughout a 4.5-year partnership, the community and research partners developed an innovative cognitive-behavioral theory (CBT) skills curriculum that could be delivered both formally and informally to overcome barriers such as the inability of previously gang-involved young men to attend groups due to conflict risks. Moreover, the CBPR partnership allowed for training and coaching to address the need for provider skill development to effectively deliver the CBT skills. CBPR partnerships increase sustainability of EBTs by cultivating participant engagement, reaching underserved participants [73], and facilitating organizational buy-in at all levels within the community organization [72].

Organizational Buy-In

Organizational "buy-in" refers to the engendered support (e.g., space, time, capital, and other resources available) of organizations and the belief that EBTs offer more advantages than disadvantages among stakeholders [74]. Garnering organizational buy-in is crucial to implementation success as it often results in a committed leadership, engagement of staff at all levels, and the provision of additional resources dedicated for the implementation of EBTs [75]. Data suggest that if an intervention is going to succeed, buy-in from all levels, including researchers, therapists, administration, communities, patients, and families affected by the mental health disorder, is needed [45, 56, 74, 76].

There are numerous ways to obtain buy-in from organization members. First, assessing that the EBT is aligned with the current priorities of the organization and the patients' needs [74, 76–78] can prevent misalignment-related barriers that arise due to competing needs. Additionally, framing the intervention as an added value to what the organization is already doing can preclude perceptions that the invention is too burdensome or not worth the investment [74]. Presenting an intervention's cost-effectiveness and ability to ease the duties of the providers, administration, and patients [74] can further solicit support among stakeholders. For example, an effective EBT may help accelerate a patient's improvement and may increase the likelihood of organizational- and provider-level investment and engagement with the treatment. Buy-in can also be enhanced by ensuring transparency throughout the implementation process. In other words, explicit communication related to expecta-

tions from staff about what will be required of them in order to deliver the intervention, listening to their concerns, and working to address those concerns can serve to boost all stakeholders' understanding and facilitate any problem-solving needed. Explaining how to use any equipment related to the intervention and receiving feedback can help providers feel heard and muster staff enthusiasm for the intervention [74]. Thus, the use of multiple methods to enhance organizational buy-in can promote the adoption of EBTs in community settings and address barriers that emerge throughout the implementation process.

Resource Support

Another way to increase sustainability of EBTs in community settings is by providing resources. Resource facilitation includes activities such as workshops, workgroups, networking, conferences, consultation or supervision, technical assistance, and mentorship, and noninteractive resources such as providing access to libraries, news and updates from the field, archived talks/slides, links to webpages, grant writing, and funding opportunities that could be provided to support the implementation of EBTs in the organization [79]. Given that most community settings are considered "resource-constricted," it is crucial to identify resources needed prior and during implementation to maximize meaningful impact [76]. Recent initiatives aim to examine the extent to which resource facilitation impacts the sustainability of EBTs. For example, Kilbourne and colleagues [80] are examining the integration of different types of resource facilitation (such as interactive resources and mentorship by research staff on how to identify barriers and influence points) and their impact on the sustainability of a statewide CBT program in school settings.

Champions

Another way to increase adoption and sustainability of EBTs in community settings is by identifying champions in the organization [76, 81]. Champions are members of the organization who are respected sources of information, are integrated with their peers in the organization, and often possess high enthusiasm for the intervention [82, 83]. They can, but do not have to, hold a position of authority or be in an administrative role. When choosing champion(s) for an intervention, the researchers and organizations need to establish clear rules and guidelines about the role of the champion, ensure that stakeholders are in agreement about who the champion(s) should be, have champion(s) at multiple levels within the organization, and provide incentives (e.g., use of space and/or small amounts of salary coverage) for the champion(s) [83].

Champions help researchers and organizations understand where the intervention falls within the group norms, local values, and realities of the local practice and

help members from the organization implement and apply the EBT-related knowledge to their clinical routine and everyday practice. For example, as champions work in the same settings and usually in similar roles as their colleagues, they are perceived as knowing what it is to "walk in the staff's shoes." This provides an insider's perspective and interactions with their colleagues that the champion can leverage to provide technical and social support when implementation barriers arise [15]. Interventions that rely on champions have been effective at influencing clinical behavior [82, 83], and research shows that champions are indispensable for maintaining enthusiasm for the EBT intervention overtime and keeping communication between stakeholders active [15].

Conclusion

Implementation-related barriers occur at multiple levels, including organizational, provider, treatment, and patient levels, with each level facing its own unique challenges as well as interacting with other difficulties cross-levels. As such, it is crucial for researchers and community organizations to systematically and strategically implement EBTs into community organizations by (1) identifying the barriers that may arise during implementation and (2) employing facilitators that target these specific barriers that were identified. This chapter highlights the importance of community-based participatory research partnerships between researchers and community organizations, as these types of collaborations help better understand, serve, provide, and advocate for some of the most vulnerable populations. By addressing emerging multilevel barriers, employing strategic facilitators, and capitalizing on equal partnerships, the adoption and sustainability of EBTs for anxiety disorders in community settings are feasible, thus decreasing the gap between science and practice.

References

1. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015;17(3):327. PMID: 26487813
2. Ougrin D. Efficacy of exposure versus cognitive therapy in anxiety disorders: systematic review and meta-analysis. BMC Psychiatry. 2011;11(1):200. https://doi.org/10.1186/1471-244X-11-200.
3. Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JA, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: a meta-analysis of randomized placebo-controlled trials. Depress Anxiety. 2018;35(6):502–14. https://doi.org/10.1002/da.22728.
4. Alonso J, Liu Z, Evans-Lacko S, Sadikova E, Sampson N, Chatterji S, Abdulmalik J, Aguilar-Gaxiola S, Al-Hamzawi A, Andrade LH, Bruffaerts R. Treatment gap for anxiety disorders is global: results of the world mental health surveys in 21 countries. Depress Anxiety. 2018;35(3):195–208. https://doi.org/10.1002/da.22711.

5. Balas EA, Boren SA. Managing clinical knowledge for health care improvement. Yearbook of medical informatics 2000: Patient-centered systems. Stuttgart, Germany: Schattauer Verlagsgesellschaft mbH; 2000.

6. DeLeon PH, Wakefield M, Hagglund KJ. The behavioral health care needs of rural communities. In: Stamm BH, editor. Rural behavioral health care: an interdisciplinary guide. 1st ed. Washington, DC: American Psychological Association; 2003. p. 23–31.

7. Lilienfeld SO, Ritschel LA, Lynn SJ, Cautin RL, Latzman RD. Science–practice gap. The encyclopedia of clinical psychology. New York, USA: Wiley-Blackwell; 2015. p. 2548–55.

8. Proctor EK, Landsverk J, Aarons G, Chambers D, Glisson C, Mittman B. Implementation research in mental health services: an emerging science with conceptual, methodological, and training challenges. Admin Pol Ment Health. 2009;36(1):24–34. https://doi.org/10.1007/s10488-008-0197-4.

9. Eccles MP, Mittman BS. Welcome to implementation science. Implement Sci. 2006;1(1):1–3. https://doi.org/10.1186/1748-5908-1-1.

10. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci. 2009;4(1):50. https://doi.org/10.1186/1748-5908-4-50.

11. Southam-Gerow MA, Rodríguez A, Chorpita BF, Daleiden EL. Dissemination and implementation of evidence based treatments for youth: challenges and recommendations. Prof Psychol Res Pr. 2012;43(5):527. https://doi.org/10.1037/a0029101.

12. Aarons GA, Wells RS, Zagursky K, Fettes DL, Palinkas LA. Implementing evidence-based practice in community mental health agencies: a multiple stakeholder analysis. Am J Public Health. 2009;99(11):2087–95. https://doi.org/10.2105/AJPH.2009.161711.

13. Schneider B, Brief AP, Guzzo RA. Creating a climate and culture for sustainable organizational change. Organ Dyn. 1996;24(4):7–19.

14. Carmazzi A, Aarons GA. Organizational culture and attitudes toward adoption of evidence-based practice. In: NASMHPD Research Institute's 2003 conference on state mental health agency services research, program evaluation, and policy; 2003 Feb 9; Baltimore, MD.

15. Curran GM, Sullivan G, Mendel P, Craske MG, Sherbourne CD, Stein MB, McDaniel A, Roy-Byrne P. Implementation of the CALM intervention for anxiety disorders: a qualitative study. Implement Sci. 2012;7(1):14. https://doi.org/10.1186/1748-5908-7-14.

16. Hadjistavropoulos HD, Nugent MM, Dirkse D, Pugh N. Implementation of internet-delivered cognitive behavior therapy within community mental health clinics: a process evaluation using the consolidated framework for implementation research. BMC Psychiatry. 2017;17(1):331. https://doi.org/10.1186/s12888-017-1496-7.

17. Glisson C, Williams NJ, Hemmelgarn A, Proctor E, Green P. Aligning organizational priorities with ARC to improve youth mental health service outcomes. J Consult Clin Psychol. 2016;84(8):713. https://doi.org/10.1037/ccp0000107.

18. Marques L, Dixon L, Valentine SE, Borba CP, Simon NM, Wiltsey SS. Providers' perspectives of factors influencing implementation of evidence-based treatments in a community mental health setting: a qualitative investigation of the training–practice gap. Psychiatr Serv. 2016;13(3):322. https://doi.org/10.1037/ser0000087.

19. Bach-Mortensen AM, Lange BC, Montgomery P. Barriers and facilitators to implementing evidence-based interventions among third sector organisations: a systematic review. Implement Sci. 2018;13(1):103. https://doi.org/10.1186/s13012-018-0789-7.

20. Mignogna J, Martin LA, Harik J, Hundt NE, Kauth M, Naik AD, Sorocco K, Benzer J, Cully J. "I had to somehow still be flexible": exploring adaptations during implementation of brief cognitive behavioral therapy in primary care. Implement Sci. 2018;13(1):76. https://doi.org/10.1186/s13012-018-0768-z.

21. Overbeck G, Kousgaard MB, Davidsen AS. The work and challenges of care managers in the implementation of collaborative care: a qualitative study. J Psychiatr Ment Health Nurs. 2018;25(3):167–75. https://doi.org/10.1111/jpm.12449.

22. Lim SS, Updike RL, Kaldjian AS, Barber RM, Cowling K, York H, Friedman J, Xu R, Whisnant JL, Taylor HJ, Leever AT. Measuring human capital: a systematic analysis of 195 countries and territories, 1990–2016. Lancet. 2018;392(10154):1217–34. https://doi.org/10.1016/S0140-6736(18)31941-X.

23. Ault-Brutus A, Lee C, Singer S, Allen M, Alegría M. Examining implementation of a patient activation and self-management intervention within the context of an effectiveness trial. Admin Pol Ment Health. 2014;41(6):777–87. https://doi.org/10.1007/s10488-013-0527-z.

24. McHugh RK, Barlow DH. The dissemination and implementation of evidence-based psychological treatments: a review of current efforts. Am Psychol. 2010;65(2):73. https://doi.org/10.1037/a0018121.

25. Pagoto SL, Spring B, Coups EJ, Mulvaney S, Coutu MF, Ozakinci G. Barriers and facilitators of evidence-based practice perceived by behavioral science health professionals. J Clin Psychol. 2007;63(7):695–705. https://doi.org/10.1002/jclp.20376.

26. Jensen-Doss A, Hawley KM, Lopez M, Osterberg LD. Using evidence-based treatments: the experiences of youth providers working under a mandate. Prof Psychol Res Pr. 2009;40(4):417. https://doi.org/10.1037/a0014690.

27. Corrigan PW, Steiner L, McCracken SG, Blaser B, Barr M. Strategies for disseminating evidence-based practices to staff who treat people with serious mental illness. Psychiatr Serv. 2001;52(12):1598–606. https://doi.org/10.1176/appi.ps.52.12.1598.

28. Langley AK, Nadeem E, Kataoka SH, Stein BD, Jaycox LH. Evidence-based mental health programs in schools: barriers and facilitators of successful implementation. School Ment Health. 2010;2(3):105–13. https://doi.org/10.1007/s12310-010-9038-1.

29. Borntrager CF, Chorpita BF, Higa-McMillan C, Weisz JR. Provider attitudes toward evidence-based practices: are the concerns with the evidence or with the manuals? Psychiatr Serv. 2009;60(5):677–81. https://doi.org/10.1176/ps.2009.60.5.677.

30. DiMeo MA, Moore GK, Lichtenstein C. Relationship of evidence-based practice and treatments: a survey of community mental health providers. J Community Psychol. 2012;40(3):341–57. https://doi.org/10.1002/jcop.20516.

31. Ruzek JI, Rosen RC. Disseminating evidence-based treatments for PTSD in organizational settings: a high priority focus area. Behav Res Ther. 2009;47(11):980–9. https://doi.org/10.1016/j.brat.2009.07.008.

32. Lim A, Nakamura BJ, Higa-McMillan CK, Shimabukuro S, Slavin L. Effects of workshop trainings on evidence-based practice knowledge and attitudes among youth community mental health providers. Behav Res Ther. 2012;50(6):397–406. https://doi.org/10.1016/j.brat.2012.03.008.

33. Lau AS. Making the case for selective and directed cultural adaptations of evidence-based treatments: examples from parent training. Clin Psychol Sci Pract. 2006;13(4):295–310. https://doi.org/10.1111/j.1468-2850.2006.00042.x.

34. Drake RE, Goldman HH, Leff HS, Lehman AF, Dixon L, Mueser KT, Torrey WC. Implementing evidence-based practices in routine mental health service settings. Psychiatr Serv. 2001;52(2):179–82. https://doi.org/10.1176/appi.ps.52.2.179.

35. Weaver T, Madden P, Charles V, Stimson G, Renton A, Tyrer P, Barnes T, Bench C, Middleton H, Wright N, Paterson S. Comorbidity of substance misuse and mental illness in community mental health and substance misuse services. Br J Psychiatry. 2003;183(4):304–13. https://doi.org/10.1192/bjp.183.4.304.

36. Griffin MG, Resick PA, Waldrop AE, Mechanic MB. Participation in trauma research: is there evidence of harm? J Trauma Stress. 2003;16(3):221–7. https://doi.org/10.1023/A:1023735821900.

37. Harned MS, Dimeff LA, Woodcock EA, Contreras I. Predicting adoption of exposure therapy in a randomized controlled dissemination trial. J Anxiety Disord. 2013;27(8):754–62. https://doi.org/10.1016/j.janxdis.2013.02.006.

38. Larsen SE, Stirman SW, Smith BN, Resick PA. Symptom exacerbations in trauma-focused treatments: associations with treatment outcome and non-completion. Behav Res Ther. 2016;77:68–77. https://doi.org/10.1016/j.brat.2015.12.009.

39. Pedersen ER, Kaysen DL, Lindgren KP, Blayney J, Simpson TL. Impact of daily assessments on distress and PTSD symptoms in trauma-exposed women. J Interpers Violence. 2014;29(5):824–45. https://doi.org/10.1177/0886260513505705.
40. Wiltsey-Stirman S, Miller CJ, Toder K, Calloway A. Development of a framework and coding system for modifications and adaptations of evidence-based interventions. Implement Sci. 2013;8(1):65. https://doi.org/10.1186/1748-5908-8-65.
41. Beidas RS, Kendall PC. Training therapists in evidence-based practice: a critical review of studies from a systems-contextual perspective. Clin Psychol Sci Pract. 2010;17(1):1–30. https://doi.org/10.1111/j.1468-2850.2009.01187.x.
42. Herschell AD, Kolko DJ, Baumann BL, Davis AC. The role of therapist training in the implementation of psychosocial treatments: a review and critique with recommendations. Clin Psychol Rev. 2010;30(4):448–66. https://doi.org/10.1016/j.cpr.2010.02.005.
43. Wiltsey-Stirman S, Gutner C, Crits-Christoph P, Edmunds J, Evans AC, Beidas RS. Relationships between clinician-level attributes and fidelity-consistent and fidelity-inconsistent modifications to an evidence-based psychotherapy. Implement Sci. 2015;10(1):115. https://doi.org/10.1186/s13012-015-0308-z.
44. Wiltsey-Stirman S, Calloway A, Toder K, Miller CJ, DeVito AK, Meisel SN, Xhezo R, Evans AC, Beck AT, Crits-Christoph P. Community mental health provider modifications to cognitive therapy: implications for sustainability. Psychiatr Serv. 2013;64(10):1056–9. https://doi.org/10.1176/appi.ps.201200456.
45. Cook JM, Biyanova T, Coyne JC. Barriers to adoption of new treatments: an internet study of practicing community psychotherapists. Admin Pol Ment Health. 2009;36(2):83–90. https://doi.org/10.1007/s10488-008-0198-3.
46. Powell BJ, Hausmann-Stabile C, McMillen JC. Mental health clinicians' experiences of implementing evidence-based treatments. J Evid Inf Soc Work. 2013;10(5):396–409. https://doi.org/10.1080/15433714.2012.664062.
47. Maslach C. Burnout: a multidimensional perspective. In: Schaufeli WB, Maslach C, Marek T, editors. Professional burnout: recent development in theory and research. London: Routledge; 2017. p. 19–32.
48. Morse G, Salyers MP, Rollins AL, Monroe-DeVita M, Pfahler C. Burnout in mental health services: a review of the problem and its remediation. Admin Pol Ment Health. 2012;39(5):341–52. https://doi.org/10.1007/s10488-011-0352-1.
49. Awa WL, Plaumann M, Walter U. Burnout prevention: a review of intervention programs. Patient Educ Couns. 2010;78(2):184–90. https://doi.org/10.1007/s10488-011-0352-1.
50. Southam-Gerow MA, Chorpita BF, Miller LM, Gleacher AA. Are children with anxiety disorders privately referred to a university clinic like those referred from the public mental health system? Admin Pol Ment Health. 2008;35(3):168–80. https://doi.org/10.1007/s10488-007-0154-7.
51. Garcia HA, McGeary CA, McGeary DD, Finley EP, Peterson AL. Burnout in veterans health administration mental health providers in posttraumatic stress clinics. Psychol Serv. 2014;11(1):50. https://doi.org/10.1037/a0035643.
52. Kim JJ, Brookman-Frazee L, Gellatly R, Stadnick N, Barnett ML, Lau AS. Predictors of burnout among community therapists in the sustainment phase of a system-driven implementation of multiple evidence-based practices in children's mental health. Prof Psychol Res Pr. 2018;49(2):132. https://doi.org/10.1037/pro0000182.
53. Youn S, Valentine SE, Patrick KA, Baldwin M, Chablani-Medley A, Aguilar Silvan Y, Shtasel D, Marques L. Practical solutions for sustaining long-term academic-community partnerships. Psychotherapy. 2018; https://doi.org/10.1037/pst0000188.
54. Varra AA, Hayes SC, Roget N, Fisher G. A randomized control trial examining the effect of acceptance and commitment training on clinician willingness to use evidence-based pharmacotherapy. J Consult Clin Psychol. 2008;76(3):449. https://doi.org/10.1037/0022-006X.76.3.449.
55. Stadnick NA, Lau AS, Barnett M, Regan J, Aarons GA, Brookman-Frazee L. Comparing agency leader and therapist perspectives on evidence-based practices: associations with indi-

vidual and organizational factors in a mental health system-driven implementation effort. Admin Pol Ment Health. 2017;45:1–5. https://doi.org/10.1007/s10488-017-0835-9.

56. Aarons GA, Sawitzky AC. Organizational climate partially mediates the effect of culture on work attitudes and staff turnover in mental health services. Admin Pol Ment Health. 2006;33(3):289. https://doi.org/10.1007/s10488-006-0039-1.

57. Gould CE, Zapata AM, Bruce J, Merrell SB, Wetherell JL, O'Hara R, Kuhn E, Goldstein MK, Beaudreau SA. Development of a video-delivered relaxation treatment of late-life anxiety for veterans. Int Psychogeriatr. 2017;29(10):1633–45. https://doi.org/10.1017/S1041610217000928.

58. Gutner CA, Suvak MK, Sloan DM, Resick PA. Does timing matter? Examining the impact of session timing on outcome. J Consult Clin Psychol. 2016;84(12):1108. https://doi.org/10.1037/ccp0000120.

59. Wolitzky-Taylor K, Zimmermann M, Arch JJ, De Guzman E, Lagomasino I. Has evidence-based psychosocial treatment for anxiety disorders permeated usual care in community mental health settings? Behav Res Ther. 2015;72:9–17. https://doi.org/10.1016/j.brat.2015.06.010.

60. Glenn D, Golinelli D, Rose RD, Roy-Byrne P, Stein MB, Sullivan G, Bystritsky A, Sherbourne C, Craske MG. Who gets the most out of cognitive behavioral therapy for anxiety disorders? The role of treatment dose and patient engagement. J Consult Clin Psychol. 2013;81(4):639. https://doi.org/10.1037/a0033403.

61. Gibbons CJ, DeRubeis RJ. Anxiety symptom focus in sessions of cognitive therapy for depression. Behav Ther. 2008;39(2):117–25. https://doi.org/10.1016/j.beth.2007.05.006.

62. Heimberg RG, Becker RE. Cognitive-behavioral group therapy for social phobia: basic mechanisms and clinical strategies. New York. New York: Guilford Press; 2002.

63. Camacho Á, Gonzalez P, Buelna C, Emory KT, Talavera GA, Castañeda SF, Espinoza RA, Howard AG, Perreira KM, Isasi CR, Daviglus ML. Anxious-depression among Hispanic/Latinos from different backgrounds: results from the Hispanic community health study/study of Latinos (HCHS/SOL). Soc Psychiatry Psychiatr Epidemio. 2015;50(11):1669–77. https://doi.org/10.1007/s00127-015-1120-4.

64. McHugh RK, Murray HW, Barlow DH. Balancing fidelity and adaptation in the dissemination of empirically-supported treatments: the promise of transdiagnostic interventions. Behav Res Ther. 2009;47(11):946–53. https://doi.org/10.1016/j.brat.2009.07.005.

65. Fuchs CH, Haradhvala N, Evans DR, Nash JM, Weisberg RB, Uebelacker LA. Implementation of an acceptance-and mindfulness-based group for depression and anxiety in primary care: initial outcomes. Fam Syst Health. 2016;34(4):386. https://doi.org/10.1037/fsh0000237.

66. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217. https://doi.org/10.1097/MLR.0b013e3182408812.

67. Gleacher AA, Olin SS, Nadeem E, Pollock M, Ringle V, Bickman L, Douglas S, Hoagwood K. Implementing a measurement feedback system in community mental health clinics: a case study of multilevel barriers and facilitators. Admin Pol Ment Health. 2016;43(3):426–40. https://doi.org/10.1007/s10488-015-0642-0.

68. Ringle VA, Read KL, Edmunds JM, Brodman DM, Kendall PC, Barg F, Beidas RS. Barriers to and facilitators in the implementation of cognitive-behavioral therapy for youth anxiety in the community. Psychiatr Serv. 2015;66(9):938–45. https://doi.org/10.1176/appi.ps.201400134.

69. Viswanathan M, Ammerman A, Eng E, Gartlehner G, Lohr KN, Griffith D, Rhodes S, Samuel-Hodge C, Maty S, Lux L, Webb L. Community-based participatory research: assessing the evidence. Evid Rep Technol Assess. 2004;99:1–8.

70. Minkler M, Wallerstein N. Community-based participatory research for health: From process to outcomes. San Francisco: Wiley; 2011.

71. Israel BA, Schulz AJ, Parker EA, Becker AB. Review of community-based research: assessing partnership approaches to improve public health. Annu Rev Public Health. 1998;19(1):173–202. https://doi.org/10.1146/annurev.publhealth.19.1.173.

72. Shalowitz MU, Isacco A, Barquin N, Clark-Kauffman E, Delger P, Nelson D, Quinn A, Wagenaar KA. Community-based participatory research: a review of the literature with strategies for community engagement. J Dev Behav Pediatr. 2009;30(4):350–61. https://doi.org/10.1097/DBP.0b013e3181b0ef14.

73. Leung MW, Yen IH, Minkler M. Community based participatory research: a promising approach for increasing epidemiology's relevance in the 21st century. Int J Epidemiol. 2004;33(3):499–506. https://doi.org/10.1093/ije/dyh010.

74. National Academies of Sciences, Engineering, and Medicine. Providing sustainable mental and neurological health care in Ghana and Kenya: workshop summary. Washington, DC: National Academies Press; 2016.

75. Breuer E, De Silva MJ, Shidaye R, Petersen I, Nakku J, Jordans MJ, Fekadu A, Lund C. Planning and evaluating mental health services in low-and middle-income countries using theory of change. Br J Psychiatry. 2016;208(s56):s55–62. https://doi.org/10.1192/bjp.bp.114.153841.

76. Buchanan D, Fitzgerald L, Ketley D, Gollop R, Jones JL, Lamont SS, Neath A, Whitby E. No going back: a review of the literature on sustaining organizational change. Int J Manag Rev. 2005;7(3):189–205. https://doi.org/10.1111/j.1468-2370.2005.00111.x.

77. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, Griffey R, Hensley M. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Admin Pol Ment Health. 2011;38(2):65–76. https://doi.org/10.1007/s10488-010-0319-7.

78. Aarons GA, Hurlburt M, Horwitz SM. Advancing a conceptual model of evidence-based practice implementation in public service sectors. Admin Pol Ment Health. 2011;38(1):4–23. https://doi.org/10.1007/s10488-010-0327-7.

79. Darnell D, Dorsey CN, Melvin A, Chi J, Lyon AR, Lewis CC. A content analysis of dissemination and implementation science resource initiatives: what types of resources do they offer to advance the field? Implement Sci. 2017;12(1):137. https://doi.org/10.1186/s13012-017-0673-x.

80. Kilbourne AM, Smith SN, Choi SY, Koschmann E, Liebrecht C, Rusch A, Abelson JL, Eisenberg D, Himle JA, Fitzgerald K, Almirall D. Adaptive school-based implementation of CBT (ASIC): clustered-SMART for building an optimized adaptive implementation intervention to improve uptake of mental health interventions in schools. Implement Sci. 2018;13(1):119. https://doi.org/10.1186/s13012-018-0808-8.

81. Youn S, Xiao H, McAleavey AA, Scofield BE, Pedersen TR, Castonguay LG, Hayes JA, Locke BD. Assessing and investigating clinicians' research interests: lessons on expanding practices and data collection in a large practice research network. Psychotherapy. 2018;56:67. https://doi.org/10.1037/pst0000192.

82. Borbas C, Morris N, McLaughlin B, Asinger R, Gobel F. The role of clinical opinion leaders in guideline implementation and quality improvement. Chest. 2000;118(2):24S–32S. https://doi.org/10.1378/chest.118.2_suppl.24S.

83. Curran GM, Thrush CR, Smith JL, Owen RR, Ritchie M, Chadwick D. Implementing research findings into practice using clinical opinion leaders: barriers and lessons learned. Jt Comm J Qual Patient Saf. 2005;31(12):700–7. https://doi.org/10.1016/S1553-7250(05)31091-9.

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